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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Hodgkin's Lymphomas

Version 4.2014

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NCCN gratefully acknowledges Dr. Elise A. Olsen for participating in the
update of the Primary Cutaneous B-Cell Lymphomas and Mycosis
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NCCN Guidelines Panel Disclosures

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Clinical Trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus.

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**NCCN Guidelines Version 4.2014 Updates
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Updates to the 4.2014 version of the NCCN Guidelines for Non-Hodgkin's Lymphomas from the 3.2014 version include:

<u>Global</u>
- New page titled, "See Special Considerations for Use of B-Cell Receptor Inhibitors (Ibrutinib and Idelalisib) (NHODG-E)" was added. A footnote was added to the appropriate pages with a link to this page.

<u>Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma</u>
- Footnote "h" was added, "Indicated for patients for whom rituximab monotherapy would be considered appropriate due to the presence of other co-morbidities (reduced renal function as measured by creatinine clearance <60 mL/min, or NCI CTCAE Grade ≥3 neutropenia or Grade ≥3 thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents.)."

CSLL-D 2 of 7 and **CSLL 5 of 7**
- CLL without del (11q) or del (17p) and CLL with del (11q):
  - ➤ Relapsed/refractory therapy, Short response for age ≥70 y
    - ◊ "Idelalisib + rituximab" was added.
  - ➤ Relapsed/refractory therapy, short response for age <70 y or older patients without significant
    - ◊ "Idelalisib + rituximab" was added.

CSLL-D 3 of 7
- CLL with del (17p):
  - ➤ **First-line therapy**
    - ◊ "Ibrutinib" was added.
  - ➤ **Relapsed/refractory therapy**
    - ◊ "Idelalisib + rituximab" was added.

<u>Follicular Lymphoma</u>
FOLL-B 1 of 3
- Second-line and Subsequent Dosing
  - ➤ "Idelalisib" was added.

Updates to the 3.2014 version of the NCCN Guidelines for Non-Hodgkin's Lymphomas from the 2.2014 version include:

<u>Peripheral T-Cell Lymphomas</u>
TCEL-B 1 of 2
- Second-line therapy:
  - ➤ For both candidate and non-candidate for transplant, "Belinostat (category 2B)" was added.

Updates to the 2.2014 version of the NCCN Guidelines for Non-Hodgkin's Lymphomas from the 1.2014 version include:

MS-1
- The Discussion sections for Follicular Lymphoma and Mantle Cell Lymphoma have been updated.

<u>Follicular lymphoma</u>
FOLL-B
- "Tositumomab/iodine I-131 tositumomab" and the corresponding references have been removed from the guidelines due to the discontinuation of this product.

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Updates to the 1.2014 version of the NCCN Guidelines for Non-Hodgkin's Lymphomas from the 2.2013 version include:

Global changes
- Suggested treatment regimen references were updated throughout the guidelines.
- "IFRT" was changed to "ISRT" throughout the algorithm.

New guidelines
PCTLD-1
- Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders guidelines were added.
LGLL-1
- T-cell Large Granular Lymphocyte Leukemia guidelines were added.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
CSLL1
- Diagnosis, Essential
  - 2nd bullet was revised and sub-bullets were added.
    - Flow cytometry of blood adequate for diagnosis of CLL/SLL (biopsy generally not required)
    - *CLL diagnosis requires presence of monoclonal B lymphocytes $\geq$ 5 x 10^9/L in peripheral blood*
    - *Clonality of B cells should be confirmed by flow cytometry*
    - Adequate immunophenotyping to establish diagnosis by flow cytometry using cell surface markers: kappa/lambda, CD19, CD20, CD5, CD23, CD10; *if flow is used to establish diagnosis, also include cytospin for cyclin D1 or FISH for t(11;14); t(11q:v)*
    - *SLL diagnosis requires presence of lymphadenopathy and/or splenomegaly with B lymphocytes $\leq$ 5 x 10^9/L in peripheral blood*
    - *SLL diagnosis should be confirmed by histopathology evaluation of lymph node biopsy*
  - 3rd bullet was revised by adding: "If diagnosis is not established by flow cytometry, then proceed with lymph node biopsy
- Diagnosis, Informative for prognostic and/or therapy determination
  - 1st bullet was revised: "FISH or stimulated cytogenetics to detect: t(11;14); t(11q;v) +12; del(11q); del(13q); del(17p)"
  - 4th bullet was added: "TP53 sequencing."
- Footnote "d" was modified by adding: "Cells of same phenotype maybe seen in reactive lymph nodes; therefore, diagnosis of SLL should only be made when effacement of lymph node architecture is seen."

CSLL-2
- Workup, "LDH' was moved from Essential to Useful Under Certain Circumstances.

CSLL-D 1 of 8
- Frail patient, significant comorbidity:
  - "Obinutuzumab + chlorambucil" was added.
  - "Chlorambucil ± rituximab" was changed to "Rituximab + chlorambucil" and "chlorambucil" was added as a monotherapy.
- CLL without del (11q) or del (17p):
  - First-line therapy, Age $\geq$70 y or younger patients with comorbidities
    - "Obinutuzumab + chlorambucil" was added.
    - "Chlorambucil ± rituximab" was changed to "Rituximab + chlorambucil " and "chlorambucil" was added as a monotherapy.
    - "Alemtuzumab" was removed.
    - "Lenalidomide" was removed.
  - Age <70 y or older patients without significant comorbidities
    - "Obinutuzumab + chlorambucil" was added.
- Footnotes:
  - Footnote was removed: "Less effective for bulky (>5 cm) lymphadenopathy; monitor for CMV reactivation." (Also for CSLL-D 4 of 8)
  - Footnote was removed: "Lenalidomide can be given as continuous or intermittent dosing for patients with CLL. Growth factors and/or dose adjustment may be needed to address cytopenias, without necessitating holding treatment..." (Also for CSLL-D 4 of 8)

CSLL-D 2 of 8
- CLL without del (11q) or del (17p):
  - Relapsed/refractory therapy, Short response for age $\geq$70 y
    - "Ibrutinib" was added.
    - "Chlorambucil ± rituximab" was changed to "Rituximab + chlorambucil."
  - Relapsed/refractory therapy, short response for age <70 y or older patients without significant comorbidities
    - "Ibrutinib" was added.
    - "R-HyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine)" was removed.
    - "Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab)" was removed.
  - Footnote "g" is new to the page: "See Special Consideration for Ibrutinib in CLL (CSLL-D 6 of 8).

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Updates to the 1.2014 version of the NCCN Guidelines for Non-Hodgkin's Lymphomas from the 2.2013 version include:

CSLL-D 3 of 8
- CLL with del (17p):
  - First-line therapy
    - "Obinutuzumab + chlorambucil" was added.
    - The regimens are now listed in alphabetical order.
  - Relapsed/refractory therapy
    - "Ibrutinib" was added.
    - "R-HyperCVAD" was removed.

CSLL-D 4 of 8
- CLL with del (11q):
  - First-line therapy, Age ≥70 y or younger patients with comorbidities,
    - "Obinutuzumab + chlorambucil" was added.
    - "Chlorambucil ± rituximab" was changed to "Rituximab + chlorambucil" and "chlorambucil" was added as a monotherapy.
    - "Alemtuzumab" was removed
    - "Lenalidomide" was removed
  - Age <70 y or older patients without significant comorbidities
    - "Obinutuzumab + chlorambucil" was added.

CSLL-D 5 of 8
- CLL with del (11q):
  - Relapsed/refractory therapy, Short response for age ≥70 y
    - "Ibrutinib" was added.
    - "Chlorambucil ± rituximab" was changed to "Rituximab + chlorambucil."
  - Relapsed/refractory therapy, short response for age <70 y or older patients without significant comorbidities
    - "Ibrutinib" was added.
    - "R-HyperCVAD" was removed.
    - "Dose-adjusted EPOCH-R" was removed.

Follicular Lymphoma
FOLL-1
- Diagnosis, Useful under certain circumstances
  - 2nd bullet was revised: "Cytogenetics or FISH: t(14;18); *BCL6 rearrangements* ~~t(8;14) or variants.~~
- Footnote "e" was revised: "~~In BCL2-negative young patients with localized disease~~ *In young patients with localized disease that lack BCL2 rearrangement or t(14;18),* consider entity of pediatric follicular lymphoma. *Analysis of BCL6 rearrangement may be useful for evaluating the diagnosis of pediatric FL.*"

FOLL-2
- Stage IIx was clarified as "Stage II bulky."

FOLL-3
- Footnote "n" was extensively revised: "Consider possibility of histologic transformation in patients with progressive disease, especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, or there are new B symptoms. If clinical suspicion of transformation, FDG-PET may help identify areas suspicious for transformation. FDG-PET scan demonstrating marked heterogeneity or sites of intense FDG avidity may indicate transformation, and biopsy should be directed biopsy at the most FDG avid area. Functional imaging does not replace biopsy to diagnose transformation. If transformation is histologically confirmed, treat with anthracycline-based therapy." (Also for FOLL-4)

FOLL-4
- Stage II bulky, III, IV:
  - After indication present, "Consider PET-CT scan" was added before initial therapy.

FOLL-5
- Stage II bulky, III, IV:
  - After initial response, "Consider PET-CT (preferred) or CT scan" was added to evaluate for response status. A corresponding footnote "r" was added: "A PET-positive PR is associated with a shortened PFS (See Discussion); however, additional treatment at this juncture has not been shown to change outcome."
  - Prior to second-line or subsequent therapy, "Consider PET-CT scan" was added to evaluate for response status with corresponding footnote "n."

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FOLL-6
- Histologic transformation to diffuse large B-cell lymphoma
  - For minimal or no prior chemotherapy,
    - See Chemotherapy regimens on BCEL-C was clarified as "first line therapy."
    - After treatment with chemotherapy + rituximab ± RT, "Consider PET-CT scan (preferred) or CT scan" was added to evaluate for response status prior to further treatment.
  - Multiple prior therapies,
    - See Chemotherapy regimens on BCEL-C was clarified as: "Selection of treatment must be highly individualized taking into acct prior treatment history."
- Footnotes
  - Footnote "t" was added: "For pathologic evaluation of histologic transformation, FISH for BCL2 rearrangement [t(14;18)] and MYC rearrangements [t(8;14) or variants, t(8;22), t(2;8)]."
  - Footnote "u" was revised: "Strongly recommend this treatment be given in the context of a clinical trial; nonmyeloablative approaches may also be considered."

FOLL-B 1 of 3
- First-line therapy:
  - "Bendamustine + rituximab" was changed from a category 2A to a category 1 recommendation.
- First-line Consolidation or Extended Dosing (optional)
  - 1st bullet was clarified: "Chemotherapy followed by radioimmunotherapy *Radioimmunotherapy (after induction with chemotherapy or chemoimmunotherapy)* (category 1)."
  - 3rd bullet was added: "If initially treated with single-agent rituximab, consolidation with rituximab 375 mg/m^2 one dose every 8 weeks for 4 doses."
- Statement was clarified: "For patients with locally bulky or *locally* symptomatic disease, consider ISRT 4-30 Gy ± additional systemic therapy."
- Footnote
  - Footnote "f" was added: "First-line consolidation with radioimmunotherapy or extended dosing of rituximab after bendamustine + rituximab has not been studied."

Gastric MALT Lymphoma
MALT-1
- Diagnosis, Useful under certain circumstances
  - 1st bullet was modified: "Molecular analysis to detect: antigen receptor gene rearrangements; *MYD88 mutation status to differentiate WM versus MZL if plasmacytic differentiation present.*" (Also for NGMLT-1, NODE-1, SPLN-1)
  - 2nd bullet was modified: "Cytogenetics or FISH: t(1;14); t(14;18); t(3;14); *t(11;14); t(11;18).*"
  - 3rd bullet was added: "FISH or PCR: t(14;18)." (Also for NGMLT-1, NODE-1, SPLN-1)
- Workup, "Endoscopy with ultrasound (if available) with multiple biopsies of anatomical sites" was moved from Essential to Useful in Selected Cases.
- Footnotes
  - Footnote "e" was modified by adding: "Locally advanced disease is more likely in patients with gastric MALT lymphoma with t(11;18), *which is less likely to respond to antibiotics.*"
  - Footnote "f" was added: "If IHC for cyclin D1 is positive, FISH for t(11;14) is not necessary."
  - Footnote "h" was added: "This is particularly useful for H. pylori-positive cases because the likelihood of tumor response is related to depth of tumor invasion."

MALT-2
- Treatment recommendations for "H. pylori positive, t(11;18) positive" were added.
- Footnote "k" was revised: "t(11;18) is a predictor for lack of *tumor* response *(<5%)* to antibiotics. *Antibiotics are used in these patients to eradicate the H. plyori infection.* These patients should be considered *for alternative therapy of the lymphoma. Liu H, Ye H, Ruskone-Fourmestraux A, et al. t(11;18) is a marker for all stage gastric MALT lymphomas that will not respond to H. pylori eradication. Gastroenterology 2002;122:1286-1294.*"

MALT-5
- Post RT recurrence has been redirected to FOLL-4.

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Updates to the 1.2014 version of the NCCN Guidelines for Non-Hodgkin's Lymphomas from the 2.2013 version include:

Nongastric MALT Lymphoma
NGMLT-2
- Stage I, II, Initial therapy
  - "Preferred" was added to "ISRT"
  - "Rituximab in selected cases" was added as a treatment option.

Mantle Cell Lymphoma
MANT-1
- Footnote "a" was revised by adding: "There are rare cases of *CCND1*-MCL (<5%) with an otherwise typical immunophenotype."

MANT-A 1 of 3
- Induction therapy, Less aggressive therapy
  - The following regimens were removed:
    - CVP (cyclophosphamide, vincristine, prednisone) + rituximab
    - Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab
- Second-line therapy
  - "Ibrutinib" was added.

Diffuse Large B-Cell Lymphoma
BCEL-1
- Diagnosis:
  - Essential, IHC panel was modified by adding, "MYC"
  - Useful Under Certain Circumstances:
    - 2nd bullet was revised by adding. "Cytogenetics or FISH: t(14;18), t(3;v), t(8;14), *t(8;v)*."
    - Bullet was removed: "Molecular analysis to detect: antigen receptor gene rearrangements; *CCND1*; *BCL2*; *BCL6*; *MYC* rearrangements by either FISH or IHC."

BCEL-3
- Stage I, II, Nonbulky (<10 cm) disease
  - The separation between "Adverse risk factors present" and "Adverse risk factors not present" was removed.
- Stage III, IV
  - "RCHOP" was modified by removing "x 6 cycles" and adding "After 2-4 cycles" prior to "See Interim Restaging (BCEL-5)."

BCEL-4
- Heading, Pre RT Evaluation" was clarified by adding: "End of induction chemoimmunotherapy."
- Follow-up imaging was changed from "CT scan no more often than every 6 mo for 2 y after completion of treatment, then only as clinically indicated" to "Repeat CT scan only as clinically indicated."

BCEL-5
- Stage III, IV
  - For responding disease, the follow-up therapy "Continue RCHOP to a total of 6 cycles" was clarified as a category 1.
  - After end-of-treatment restaging with a complete response, "Consider RT to initially bulky disease" was changed from a category 2B to a category 2A recommendation.

BCEL-B 1 of 2
- 2nd bullet was modified by adding other treatment options:
  - Optimal first-line therapy is more controversial than other subtypes of NHL; *however, treatment regimens include:*
    - *RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) x 6 cycles + RT*
    - *Dose-adjusted EPOCH-R ([etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin] + rituximab) x 6-8 cycles; for persistent focal disease, RT can be added.*
    - *RCHOP x 4 cycles followed by ICE (ifosfamide, carboplatin, etoposide) x 3 cycles ± RT (category 2B)*
- The following bullet was removed: "Because of relative rarity of PMBL, the role of RCHOP-21 is not established as the definitive treatment option for this disease. However, RCHOP-21 is widely used in NCCN institutions based on data in DLBCL and other regimens have been used (see BCEL-C). There are data suggesting that more intense therapy may be better based on non-randomized comparisons."

BCEL-C 1 of 4
- The treatment regimen group for "First-line Therapy for Patients with Poor Left Ventricular Function" was modified to include "*or very frail.*"
- "R-mini-CHOP" was added under a separate heading "Patients >80 years of age with comorbidities."

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Updates to the 1.2014 version of the NCCN Guidelines for Non-Hodgkin's Lymphomas from the 2.2013 version include:

Burkitt Lymphoma
BURK-1
- Diagnosis:
  - "Cytogenetics ± FISH: t(8;14) or variants; MYC" was moved from Useful Under Certain Circumstances to Essential.

AIDS-Related B-cell Lymphomas
AIDS-1
- Diagnosis, Useful Under Certain Circumstances
  - "CD30 for PEL" was added to additional immunohistochemical studies to establish lymphoma subtype.

AIDS-2
- Burkitt lymphoma:
  - Suggested regimens,
    - 1st subbullet was modified by removing, "Dose-adjusted EPOCH + rituximab (preferred)."
    - A note was added to indicate the regimens are listed in alphabetical order.
  - Footnote
    - Footnote "d" was changed from "Patients on active antiretrovirals being treated with a rituximab-based regimen with persistently low CD4 count of <100 tend to have poor prognosis and higher risk of infection" to "In patients on active antiretrovirals treated with rituximab-based regimens, low CD4 count (<100/mcL) may be associated with decreased response and survival outcomes; CD4 count <50/mcL has been associated with increased treatment-related deaths."

Primary Cutaneous B-Cell Lymphomas
CUTB-1
- Diagnosis:
  - Useful Under Certain Circumstances
    - 3rd bullet was revised, "If adequate biopsy material available, flow cytometry *or PCR* can be useful in determining B-cell clonality."
    - Bullet was removed, "Molecular analysis to detect: antigen receptor gene rearrangements; *IG* gene rearrangement by PCR."

Peripheral T-Cell Lymphomas
TCEL-1
- Diagnosis, Useful Under Certain Circumstances
  - 2nd bullet was modified by adding, "Additional immunohistochemical studies to establish lymphoma subtype: βF1, *TCR-CγM1*, CD279/PD1, CXCL-13."

TCEL-3
- Induction Therapy:
  - The treatment recommendations for all stages of PTCL, NOS; ALCL, ALK -; AITL, EATL have been combined and the follow-up therapy page for Stage I, II Low/Low-Intermediate disease has been removed.
  - For multiagent chemotherapy, the number of cycles has been changed from "8" cycles to "6" cycles.
  - The radiation dose "30-40 Gy for locoregional disease" was added as appropriate.
- The bullets related to breast implant-associated ALCL have been extensively revised.

TCEL-B 1 of 2
- First-line therapy:
  - For other histologies, "CHOP followed by IVE (ifosfamide, etoposide, epirubicin) alternating with intermediate-dose methotrexate [Newcastle Regimen]" was clarified by adding "studied only in patients with EATL."
- Second-line therapy:
  - For both candidate and non-candidate for transplant, "Brentuximab vedotin for CD30+ PTCL (category 2B)" was added.

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Updates to the 1.2014 version of the NCCN Guidelines for Non-Hodgkin's Lymphomas from the 2.2013 version include:

Mycosis Fungoides/Sezary Syndrome
MFSS-1
- Diagnosis:
  - Useful Under Certain Circumstances,
    - 1st bullet, IHC panel of skin biopsy, "TCR-CγM1" was added.
    - 4th bullet, the flow cytometry details were moved from the workup section to the 2nd sub-bullet.

MFSS-2
- TNMB table:
  - Blood category, B2 was modified by adding, "...<u>or</u> *CD4/CD8 ≥ 10 or ≥40% CD4+/CD7- or ≥30% CD4+/CD26- cells.*"

MFSS-A 1 of 4
- Skin-directed Therapies:
  - Limited/localized skin involvement, 3rd bullet was modified as, "Local radiation (~~12-36~~ *8-36* Gy)."
- Systemic Therapies
  - Category B, Second-line therapies, "bortezomib" was removed.

Adult T-cell Leukemia/Lymphoma
ATLL-1
- Diagnosis, Useful Under Certain Circumstances
  - 3rd subbullet was modified by adding, "If biopsy performed, the recommended panel for paraffin section immunohistochemistry: CD3, CD4, CD7, CD8, CD25, *and CD30.*"
- The table "Diagnostic Criteria and Classification of Clinical Subtypes of ATLL" was removed and is cited in footnote "d" as "Shimoyama M and members of The Lymphoma Study Group. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the Lymphoma Study Group (1984-87). Br J Haematol 1991;79:428-437."

Extranodal NK/T-cell Lymphoma, nasal type
NKTL-1
- Diagnosis:
  - IHC panel was revised and moved from Essential to Useful Under Certain Circumstances
    - B-cell lineage: CD20
    - T-cell lineage: CD2, CD7, CD8, CD4, CD5
    - ~~NK lineage: CD56;~~ Other: CD30, Ki-67
- Workup, Essential
  - "Concurrent referral to RT for pre-treatment evaluation" was added.

T-cell Prolymphocytic Leukemia
TPLL-2
- Primary treatment, "IV alemtuzumab preferred" was removed and "Intravenous" was added as the recommended route of administration for alemtuzumab.

Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-cell and NK/T-cell Neoplasms
NHODG-A 4 of 11
- "MYD88 mut" was added to the algorithm to differentiate between LPL and MZL.
- For HCL, "Confirmation with BRAF sequencing or IHC for mutant protein" was added.

Supportive Care for NHL
NHODG-B 2 of 3
- Hepatitis B virus (HBV)
  - 3rd bullet was revised: "Prophylactic antiviral therapy *with entecavir* is recommended for..."
  - 3rd bullet,
    - 1st sub-bullet was added: "Entecavir is preferred based on Huang YH, et al. J Clin Oncol 2013;31:2765-2772; Huang H, et al. J Clin Oncol 2013;31:Abstract 8503."
    - 3rd sub-bullet, 2nd tertiary bullet was revised: "If viral load fails to drop *or previously undetectable PCR becomes positive*, consult hepatologist *and discontinue anti-CD20 antibody therapy*."

Principles of Radiation Therapy
NHODG-D (1 of 2)
- General dose guidelines, "Primary cutaneous anaplastic large cell lymphoma: 30-36 Gy" was added.

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CLL/SLL[a]

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DIAGNOSIS

ESSENTIAL:

- **Hematopathology review of all slides with at least one paraffin block representative of the tumor, if the diagnosis was made on a lymph node or bone marrow biopsy. Rebiopsy if consult material is nondiagnostic.**
- **Flow cytometry of blood adequate for diagnosis of CLL/SLL (biopsy generally not required)**
  - ➤ **CLL diagnosis requires presence of monoclonal B lymphocytes ≥ 5 x 10^9/L in peripheral blood**
  - ➤ **Clonality of B cells should be confirmed by flow cytometry**
  - ➤ **Adequate immunophenotyping to establish diagnosis by flow cytometry using cell surface markers:[b,c] kappa/lambda, CD19, CD20, CD5, CD23, CD10; if flow is used to establish diagnosis, also include cytospin for cyclin D1 or FISH for t(11;14); t(11q;v)**
  - ➤ **SLL diagnosis requires presence of lymphadenopathy and/or splenomegaly with B lymphocytes ≤5 x 10^9/L in peripheral blood**
  - ➤ **SLL diagnosis should be confirmed by histopathology evaluation of lymph node biopsy**
- **If diagnosis is not established by flow cytometry, then proceed with lymph node biopsy. An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry) may be sufficient for diagnosis.**
  - ➤ **Adequate immunophenotyping to establish diagnosis by IHC panel:[b,c] CD3, CD5, CD10, CD20, CD23, cyclin D1**
- **Absolute monoclonal B lymphocyte count[d]**

INFORMATIVE FOR PROGNOSTIC AND/OR THERAPY DETERMINATION:[e]
- **FISH or stimulated cytogenetics to detect: +12; del(11q); del(13q); del(17p)**
- **Molecular analysis to detect: IGHV mutation status**
- **Determination of CD38 and ZAP-70 expression by flow cytometry or immunohistochemistry[f]**
- **TP53 sequencing**

CLL/SLL ⟶ See Workup for CLL/SLL (CSLL-2)

Monoclonal B-cell lymphocytosis (MBL)
- **Absolute monoclonal B lymphocyte count <5000/mm^3**
- **All lymph nodes <1.5 cm**
- **No anemia**
- **No thrombocytopenia**

⟶ **Observe**

[a]CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma. Cases diagnosed as B-PLL are excluded from this guideline.
[b]Typical immunophenotype: CD5+, CD23+, CD43+/-, CD10-, CD19+, CD20 dim, sIg dim+ and cyclin D1-. Note: Some cases may be sIg bright+, CD23- or dim, and some MCL may be CD23+; cyclin D1 immunohistochemistry or FISH for t(11;14) should be considered in all cases and should be done in cases with an atypical immunophenotype (CD23 dim or negative, CD20 bright, sIg bright).

[c]See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).
[d]Absolute monoclonal B lymphocyte count <5000/mm^3 in the absence of adenopathy or other clinical features of lymphoproliferative disorder is MBL. Cells of same phenotype may be seen in reactive lymph nodes; therefore, diagnosis of SLL should only be made when effacement of lymph node architecture is seen.
[e]See Prognostic Information for CLL (CSLL-A).
[f]Evaluation of ZAP-70 expression can be challenging and ZAP-70 is not recommended outside the setting of a clinical trial.

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WORKUP

ESSENTIAL:
- **Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen**
- **Performance status**
- **B symptoms**
- **CBC, differential, platelets**
- **Comprehensive metabolic panel**
- **Hepatitis B testing [g] if CD20 monoclonal antibody contemplated**
- **MUGA scan/echocardiogram if anthracycline- or anthracenedione-based regimen is indicated**
- **Pregnancy testing in women of child-bearing age (if chemotherapy planned)**

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- **Quantitative immunoglobulins**
- **Reticulocyte count, haptoglobin, and direct Coombs' test**
- **Chest/abdominal/pelvic CT should be done prior to initiation of therapy (particularly when peripheral adenopathy is present and symptoms suggest bulky lymph nodes)**
- **Beta-2-microglobulin**
- **LDH**
- **Uric acid**
- **Unilateral bone marrow biopsy (± aspirate) at initiation of therapy**
- **Discussion of fertility issues and sperm banking**
- **PET scan is generally not useful in CLL but can assist in directing nodal biopsy if Richter's transformation is suspected**

SLL/Localized
(Ann Arbor Stage I)
(See CSLL-3)

CLL or SLL
(Ann Arbor Stage II - IV,
Rai Stages 0-IV)
(See CSLL-3)

[g] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

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PRESENTATION

SLL/Localized (Ann Arbor Stage I)[h] → **Locoregional RT (if indicated)** → **Observe**

See Supportive Care for Patients with CLL (CSLL-C)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

CLL (Rai Stages 0-IV) or SLL (Ann Arbor Stages II-IV)[h]

SLL

CLL Rai Low (0) and Intermediate (I-II) risk[i]

Evaluate for indications for treatment:[j]
- Eligible for clinical trial[k]
- Significant disease-related symptoms:
  ➤ Fatigue (severe)
  ➤ Night sweats
  ➤ Weight loss
  ➤ Fever without infection
- Threatened end-organ function
- Progressive bulky disease (spleen >6 cm below costal margin, lymph nodes >10 cm)
- Progressive anemia
- Progressive thrombocytopenia[l]

No indication → Observe

Indication present

Frail patients, significant comorbidity[n] → **See CSLL-4**

Patients with adequate functional status[n] →
- Evaluate FISH[o]
- Imaging as appropriate

CLL Without Deletion of 11q or 17p (See CSLL-5)

CLL With Deletion of 17p (See CSLL-6)

CLL With Deletion of 11q (See CSLL-7)

CLL Rai High (III-IV) Risk[i]

Histologic transformation to diffuse large-cell/Hodgkin lymphoma → **Manage as aggressive lymphoma (See BCEL-C)[m]** → **Consider allogeneic stem cell transplant (See BCEL-C)**

[h]See Supportive Care for Patients with CLL (CSLL-C).
[i]See Rai and Binet Classification Systems (CSLL-B).
[j]Absolute lymphocyte count alone is not an indication for treatment unless above 200-300 x 10^9/L or symptoms related to leukostasis.
[k]Given incurability with conventional therapy, consider a clinical trial as first line of treatment.

[l]Platelet counts >100,000 cells/mm^3 are typically not associated with clinical risk.
[m]In addition to the regimens listed in BCEL-C, R-HyperCVAD has also been used in this setting.
[n]Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. J Am Geriatr Soc 2008;56:1926-1931.
[o]Re-evaluation of FISH [t(11;14); t(11q;v); +12; del(11q); del(13q); del(17p)] is necessary to direct treatment.

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FRAIL PATIENTS, SIGNIFICANT COMORBIDITY

	FIRST-LINE THERAPY	**RELAPSED/ REFRACTORY THERAPY[p]**

See Supportive Care for Patients with CLL (**CSLL-C**)

Consider prophylaxis for tumor lysis syndrome (**See NHODG-B**)

See monoclonal antibody and viral reactivation (**NHODG-B**)

Frail patients, significant comorbidity[n] (not able to tolerate purine analogs)[h,j,k] → See Suggested Regimens (**CSLL-D 1 of 7**) ———→ See Suggested Regimens (**CSLL-D 2 of 7**)

[h] See Supportive Care for Patients with CLL (CSLL-C).
[j] Absolute lymphocyte count alone is not an indication for treatment unless above 200-300 x 10^9/L or symptoms related to leukostasis.
[k] Given incurability with conventional therapy, consider a clinical trial as first line of treatment.
[n] Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. J Am Geriatr Soc 2008;56:1926-1931.
[p] If long response, treat with the same first-line therapy. If short response, consider alternative first-line therapy not used before.

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CLL WITHOUT DELETION OF 11q or 17p

| See Supportive Care for Patients with CLL (CSLL-C) |
| Consider prophylaxis for tumor lysis syndrome (See NHODG-B) |
| See monoclonal antibody and viral reactivation (NHODG-B) |

FIRST-LINE THERAPY

RESPONSE TO THERAPY[q,r]

RELAPSED/ REFRACTORY THERAPY

CLL without del (11q) or del (17p)[h,j,k]

→ Age ≥70 y or younger patients with comorbidities[n]
→ See Suggested Regimens (CSLL-D 1 of 7)

→ Long response,[s] repeat FISH, if del (17p) see CSLL-6, or del (11q) see CSLL-7 → Retreat with first-line therapy until a short response

→ Short response,[s] repeat FISH, if del (17p) see CSLL-6, or del (11q) see CSLL-7 → See Suggested Regimens (CSLL-D 2 of 7) (relapsed/refractory therapy) → Consider allogeneic stem cell transplant, if without significant comorbidities[q]

→ Age <70 y or older without significant comorbidities[n]
→ See Suggested Regimens (CSLL-D 1 of 7)

→ Long response,[s] repeat FISH, if del (17p) see CSLL-6, or del (11q) see CSLL-7 → Retreat with first-line therapy until a short response

→ Short response,[s] repeat FISH, if del (17p) see CSLL-6, or del (11q) see CSLL-7 → See Suggested Regimens (CSLL-D 2 of 7) (relapsed/refractory therapy) → Allogeneic stem cell transplant

[h] See Supportive Care for Patients with CLL (CSLL-C).

[j] Absolute lymphocyte count alone is not an indication for treatment unless above 200-300 x 10^9/L or symptoms related to leukostasis.

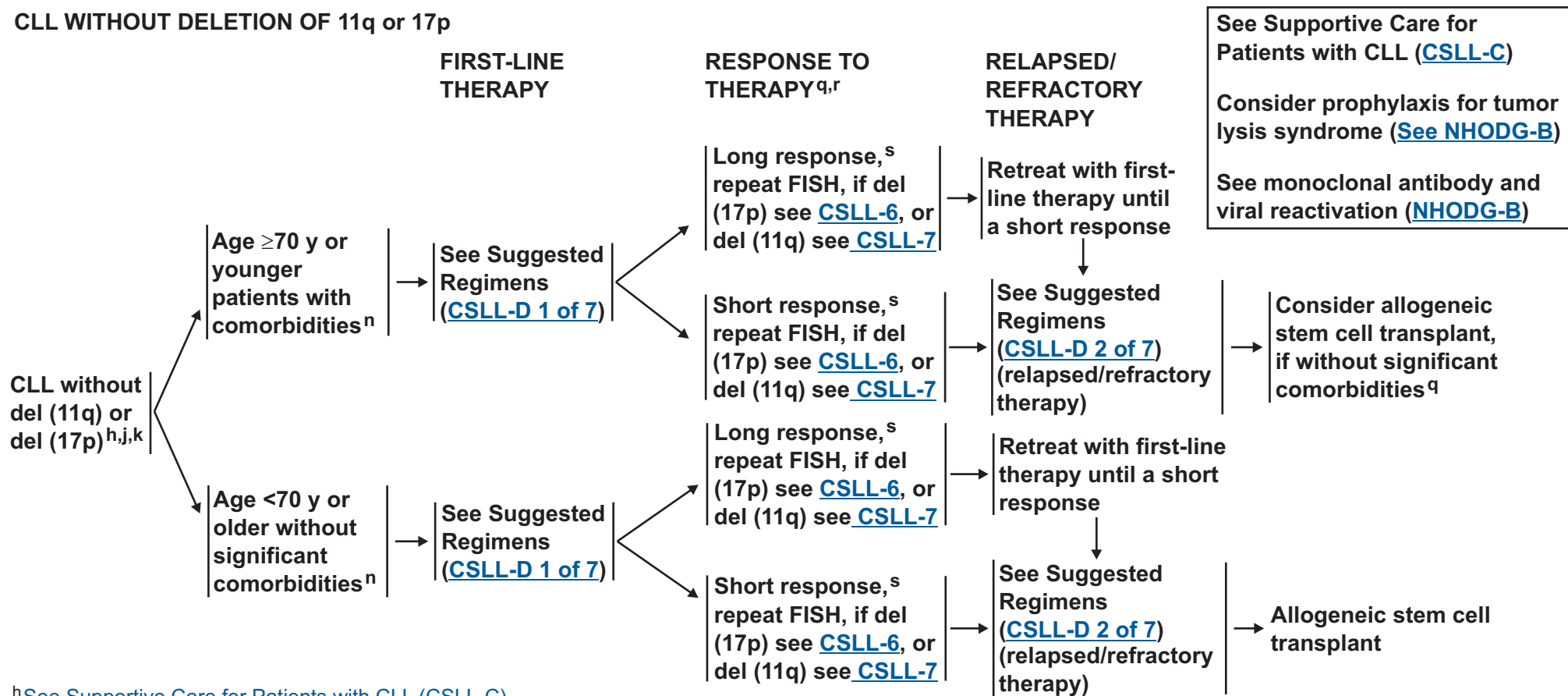[k] Given incurability with conventional therapy, consider a clinical trial as first line of treatment.

[n] Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. J Am Geriatr Soc 2008;56:1926-1931.

[q] Keating M, Wierda W, Tam C, et al. Long term outcome following treatment failure of FCR chemoimmunotherapy as initial therapy for chronic lymphocytic leukemia [abstract]. Blood 2009;114:Abstract 2381.
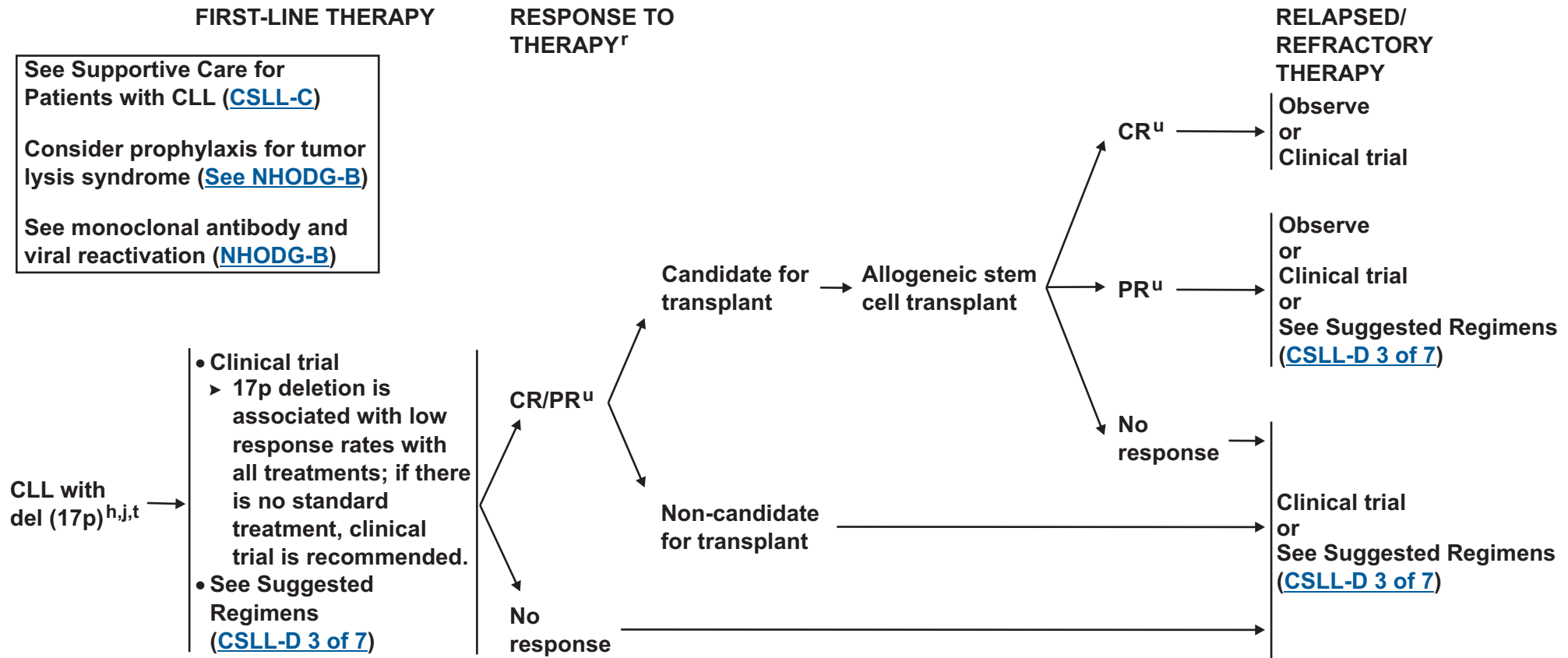
[r] Isolated progressive lymphocytosis in the setting of reduced lymph node size or organomegaly or improvement in hemoglobin/platelets will not be considered progressive disease.

[s] Long and short response cannot be rigorously defined based on available data. A major factor is that the definition would be influenced by the prior treatment. Clinicians will need to use clinical judgement. For instance, after a regimen such as FCR, 3 years may be a reasonable cutoff based on the data from MDACC. However, after chlorambucil, 18-24 months may be a reasonable cutoff.

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CLL WITH DELETION OF 17p

FIRST-LINE THERAPY

RESPONSE TO THERAPY[r]

RELAPSED/ REFRACTORY THERAPY

See Supportive Care for Patients with CLL (**CSLL-C**)

Consider prophylaxis for tumor lysis syndrome (**See NHODG-B**)

See monoclonal antibody and viral reactivation (**NHODG-B**)

CLL with del (17p)[h,j,t] →

- Clinical trial
  - 17p deletion is associated with low response rates with all treatments; if there is no standard treatment, clinical trial is recommended.
- See Suggested Regimens (**CSLL-D 3 of 7**)

CR/PR[u] →
- Candidate for transplant → Allogeneic stem cell transplant →
  - **CR[u]** → Observe or Clinical trial
  - **PR[u]** → Observe or Clinical trial or See Suggested Regimens (**CSLL-D 3 of 7**)
  - **No response** → Clinical trial or See Suggested Regimens (**CSLL-D 3 of 7**)
- Non-candidate for transplant → Clinical trial or See Suggested Regimens (**CSLL-D 3 of 7**)

No response → Clinical trial or See Suggested Regimens (**CSLL-D 3 of 7**)

[h] See Supportive Care for Patients with CLL (CSLL-C).

[j] Absolute lymphocyte count alone is not an indication for treatment unless above 200-300 x 10^9/L or symptoms related to leukostasis.

[r] Isolated progressive lymphocytosis in the setting of reduced lymph node size or organomegaly or improvement in hemoglobin/platelets will not be considered progressive disease.
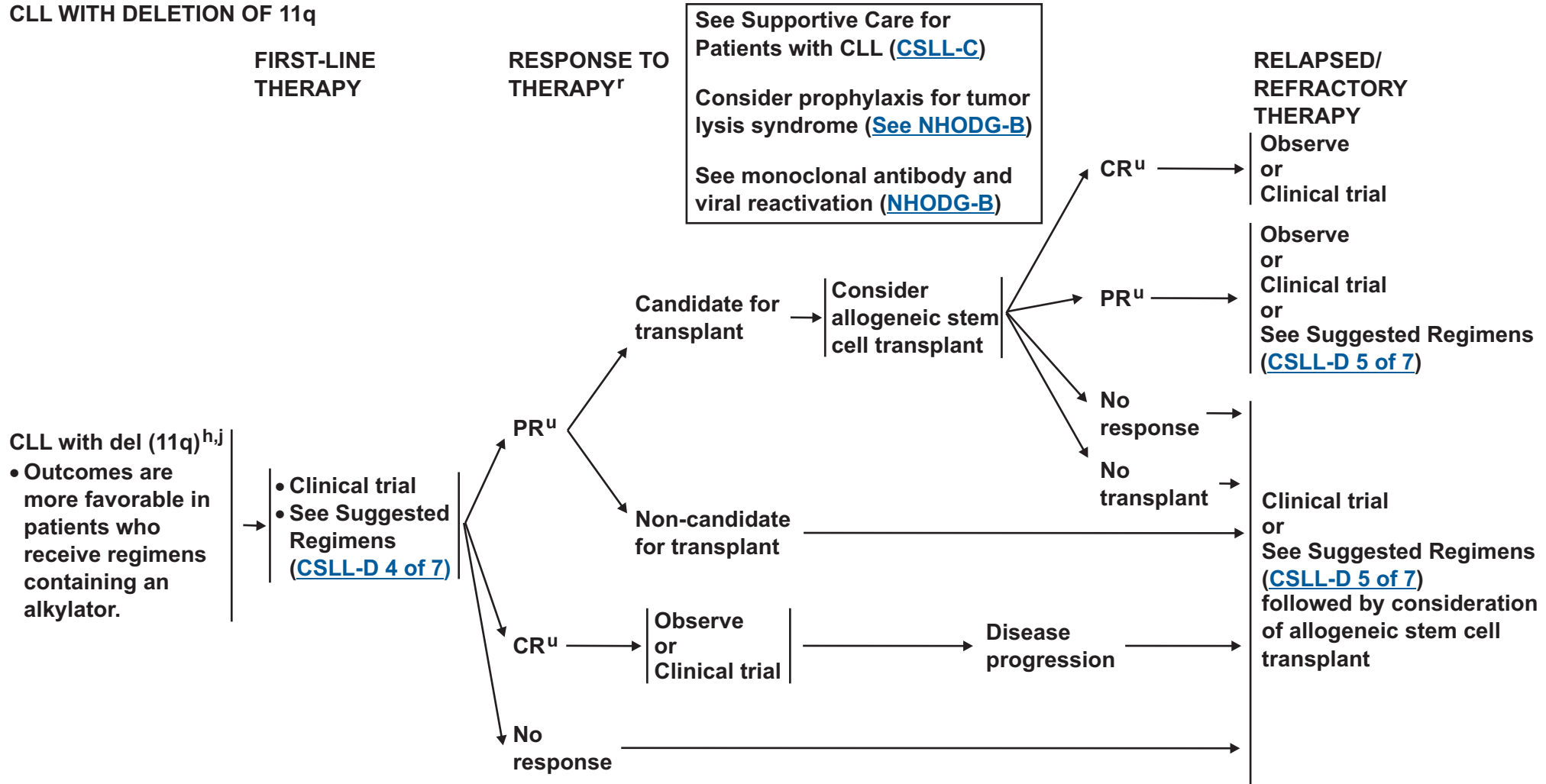
[t] Patients with low positivity should be retested due to chance of false-positive results.

[u] See Response Criteria: CLL (CSLL-E) or SLL (NHODG-C).

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CLL WITH DELETION OF 11q

FIRST-LINE THERAPY

RESPONSE TO THERAPY[r]

RELAPSED/ REFRACTORY THERAPY

See Supportive Care for Patients with CLL (CSLL-C)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

CLL with del (11q)[h,j]
- Outcomes are more favorable in patients who receive regimens containing an alkylator.

- Clinical trial
- See Suggested Regimens (CSLL-D 4 of 7)

PR[u]

Candidate for transplant → Consider allogeneic stem cell transplant

- CR[u] → Observe or Clinical trial
- PR[u] → Observe or Clinical trial or See Suggested Regimens (CSLL-D 5 of 7)
- No response →
- No transplant →

Non-candidate for transplant →

CR[u] → Observe or Clinical trial → Disease progression →

No response →

Clinical trial or See Suggested Regimens (CSLL-D 5 of 7) followed by consideration of allogeneic stem cell transplant

---

[h] See Supportive Care for Patients with CLL (CSLL-C).

[j] Absolute lymphocyte count alone is not an indication for treatment unless above 200-300 x 10^9/L or symptoms related to leukostasis.

[r] Isolated progressive lymphocytosis in the setting of reduced lymph node size or organomegaly or improvement in hemoglobin/platelets will not be considered progressive disease.

[u] See Response Criteria: CLL (CSLL-E) or SLL (NHODG-C).

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PROGNOSTIC INFORMATION FOR CLL[a]

Immunoglobulin Heavy-Chain Variable (IGHV) Region Gene Mutation and Surrogates by Flow Cytometry

| | Outcome Association | |
	Favorable	Unfavorable
DNA sequencing[b]		
IGHV	>2% mutation	≤2% mutation
Flow Cytometry		
CD38	<30%	≥30%
Zap 70	<20%	≥20%

Interphase Cytogenetics (FISH)[c]

Unfavorable	Neutral	Favorable
del(11q) del(17p)	Normal +12	del(13q) (as a sole abnormality)

[a]This table provides useful prognostic information relative to the time to progression where therapy is required and survival. The presence of del(11q) and/or del(17p) are associated with short progression-free survival to chemotherapy and chemoimmunotherapy approaches. Alemtuzumab or high-dose steroids have response in del(17p) disease.

[b]IGHV rearrangements involving VH3-21 carry a poor prognosis even if mutated.

[c]Formal studies identifying the percentage of abnormal cells identified by FISH are ongoing, although populations less than 10% appear to not have the clinical impact as noted in the table.

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CLL STAGING SYSTEMS

Rai System[a]

Stage	Description	Risk Status
0	Lymphocytosis, lymphocytes in blood >15,000/mcL and >40% lymphocytes in the bone marrow	Low
I	Stage 0 with enlarged node(s)	Intermediate
II	Stage 0-I with splenomegaly, hepatomegaly, or both	Intermediate
III[c]	Stage 0-II with hemoglobin <11.0 g/dL or hematocrit <33%	High
IV[c]	Stage 0-III with platelets <100,000/mcL	High

Binet System[b]

Stage	Description
A	Hemoglobin ≥10 g/dL and Platelets ≥100,000/mm^3 and <3 enlarged areas
B	Hemoglobin ≥10 g/dL and Platelets ≥100,000/mm^3 and ≥3 enlarged areas
C[c]	Hemoglobin <10 g/dL and/or Platelets <100,000/mm^3 and any number of enlarged areas

[a] This research was originally published in Blood. Rai KR, Sawitsky A, Cronkite EP, Chanana AD, Levy RN, Pasternack BS. Clinical staging of chronic lymphocytic leukemia. Blood 1975;46(2):219-234. (c) The American Society of Hematology.

[b] From: Binet JL, Auquier A, Dighiero G, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer 1981;48:198-206.

[c] Immune-mediated cytopenias are not the basis for these stage definitions.

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SUPPORTIVE CARE FOR PATIENTS WITH CLL

Recurrent Sinopulmonary Infections (requiring IV antibiotics or hospitalization)	• **Antimicrobials as appropriate**
	• **Evaluate serum IgG, if <500 mg/dL**
	  ➤ **begin monthly IVIG 0.3-0.5 g/kg,**
	  ➤ **adjust dose/interval to maintain nadir level of approximately 500 mg/dL**

Antiinfective Prophylaxis	• **Recommended for patients receiving purine-analog and/or alemtuzumab during treatment and thereafter, if tolerated**
	  ➤ **Herpes virus (acyclovir or equivalent)**
	  ➤ **PCP (sulfamethoxazole/trimethoprim or equivalent)**
	• **Alemtuzumab: Clinicians must be aware of the high risk of CMV reactivation. The current appropriate management is controversial; some use ganciclovir (oral or IV) prophylactically if viremia is present, others use ganciclovir only if viral load is rising. CMV viremia should be measured by PCR quantitation at least every 2-3 wks. Consultation with an infectious disease expert may be necessary.**
	
	• **Recommend HBV prophylaxis and monitoring in high-risk patients receiving anti-CD20 monoclonal antibodies and alemtuzumab. See** Supportive Care for NHL (NHODG-B) **for details on the management of infections.**

Autoimmune Cytopenias	• **Autoimmune hemolytic anemia (AIHA): Diagnosis with reticulocyte count, haptoglobin, DAT** ➤ **AIHA that develops in setting of treatment with fludarabine: stop, treat, and avoid subsequent fludarabine** • **Immune thrombocytopenic purpura (ITP): Evaluate bone marrow for cause of low platelets** • **Pure red cell aplasia (PRCA): Evaluate for parvo B19 and bone marrow evaluation** • **Treatment: Corticosteroids, rituximab, IVIG, cyclosporin A, splenectomy, eltrombopag, or romiplostim (ITP)**
Vaccination	• **Annual influenza vaccine[a]** • **Pneumococcal vaccine (Prevnar preferred) every 5 yrs** • **Avoid all live vaccines, including Zoster**
Blood Product Support	• **Transfuse according to institutional or published standards** • **Irradiate all blood products to avoid transfusion-associated GVHD**

[a] In patients who have received rituximab, B-cell recovery occurs by approximately 9 months. Prior to B-cell recovery, patients generally do not respond to influenza vaccine and if given should not be considered vaccinated.

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SUPPORTIVE CARE FOR PATIENTS WITH CLL

Tumor Lysis Syndrome (TLS)	• **Consider tumor prophylaxis measures in patients with bulky disease at high risk for TLS.** ➤ **For details on the symptoms, prophylaxis, and management of TLS in NHL, see Supportive Care for NHL (NHODG-B).**
Tumor Flare Reactions	• **Management of tumor flare recommended for patients receiving lenalidomide** • **Tumor flare reactions:** ➤ **Painful lymph node enlargement or lymph node enlargement with evidence of local inflammation, occurring with treatment initiation; may also be associated with spleen enlargement, low-grade fever, and/or rash** • **Treatment:** ➤ **Steroids (eg, prednisone 25-50 mg PO for 5-10 days)** ➤ **Antihistamines for rash and pruritus (cetirizine 10 mg PO QID or loratadine 10 mg PO daily)** • **Prophylaxis:** ➤ **Consider in patients with bulky lymph nodes (>5 cm)** ➤ **Steroids (eg, prednisone 20 mg PO for 5-7 days followed by rapid taper over 5-7 days)**
Thromboprophylaxis	• **Recommended for prevention of thromboembolic events in patients receiving lenalidomide:** ➤ **Aspirin 81 mg daily if platelets above 50×10^{12}/L** • **Note that the above may differ from the NCCN Guidelines for Venous Thromboembolic Disease in which the recommendations with lenalidomide pertain only to patients with multiple myeloma**

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SUGGESTED TREATMENT REGIMENS[a]
(in order of preference)

CLL without del (11q) or del (17p)

Frail patient, significant comorbidity
  (not able to tolerate purine analogs)

- Obinutuzumab + chlorambucil
- Rituximab + chlorambucil
- Rituximab
- Pulse corticosteroids
- Chlorambucil

See Supportive Care for
Patients with CLL (CSLL-C)

Consider prophylaxis for tumor
lysis syndrome (See NHODG-B)

See monoclonal antibody and
viral reactivation (NHODG-B)

First-line therapy[b]

- Age ≥70 y or younger patients with comorbidities
  - ➤ Obinutuzumab + chlorambucil
  - ➤ Rituximab + chlorambucil
  - ➤ Bendamustine (70 mg/m^2 in cycle 1 with escalation to 90 mg/m^2 if tolerated) ± rituximab
  - ➤ Cyclophosphamide, prednisone ± rituximab
  - ➤ Rituximab
  - ➤ Fludarabine[c,d,e] ± rituximab
  - ➤ Cladribine
  - ➤ Chlorambucil
- Age <70 y or older patients without significant comorbidities
  - ➤ Chemoimmunotherapy
    - ◇ FCR[c] (fludarabine,[e] cyclophosphamide, rituximab)
    - ◇ FR[c] (fludarabine,[e] rituximab)
    - ◇ PCR (pentostatin, cyclophosphamide, rituximab)
    - ◇ Bendamustine ± rituximab
    - ◇ Obinutuzumab + chlorambucil

Relapsed/Refractory therapy

See Suggested Regimens
for Relapsed/Refractory
therapy for CLL without del
(11q) or del (17p) (2 of 7)

See Suggested Regimens for CLL with del (17p) (3 of 7)
See Suggested Regimens for CLL with del (11q) (4 of 7)

[a]See references for regimens CSLL-D 6 of 7 and CSLL-D 7 of 7.
[b]See Supportive Care for Patients with CLL (CSLL-C).
[c]Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.
[d]In patients ≥70 y, fludarabine does not appear to have a benefit for first-line therapy over other therapies including chlorambucil.
[e]See Discussion for further information on oral fludarabine.

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SUGGESTED TREATMENT REGIMENS[a]
(in order of preference)

CLL without del (11q) or del (17p)

Relapsed/Refractory therapy[b]

- **Long response[f]**
  - ➤ Retreat as in first-line therapy until short response

- **Short response[f] for age ≥70 y (repeating therapy used in immediate prior line not recommended)**
  - ➤ Ibrutinib[g]
  - ➤ Idelalisib + rituximab[g,h]
  - ➤ Chemoimmunotherapy
    - ◇ Reduced-dose FCR[c,e]
    - ◇ Reduced-dose PCR
    - ◇ Bendamustine ± rituximab
    - ◇ High-dose methylprednisolone (HDMP) + rituximab
    - ◇ Rituximab + chlorambucil
  - ➤ Ofatumumab
  - ➤ Lenalidomide[i] ± rituximab
  - ➤ Alemtuzumab[j] ± rituximab
  - ➤ Dose-dense rituximab (category 2B)

- **Short response[f] for age <70 y or older patients without significant comorbidities (repeating therapy used in immediate prior line not recommended)**
  - ➤ Ibrutinib[g]
  - ➤ Idelalisib + rituximab[g,h]
  - ➤ Chemoimmunotherapy
    - ◇ FCR[c,e]
    - ◇ PCR
    - ◇ Bendamustine ± rituximab
    - ◇ Fludarabine[c,e] + alemtuzumab
    - ◇ RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)
    - ◇ OFAR[c] (oxaliplatin, fludarabine,[e] cytarabine, rituximab)
  - ➤ Ofatumumab
  - ➤ Lenalidomide[i] ± rituximab
  - ➤ Alemtuzumab[j] ± rituximab
  - ➤ HDMP + rituximab

See Supportive Care for Patients with CLL (CSLL-C)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

See Suggested Regimens for CLL with del (17p) (3 of 7)

See Suggested Regimens for CLL with del (11q) (4 of 7)

[a] See references for regimens CSLL-D 6 of 7 and CSLL-D 7 of 7.
[b] See Supportive Care for Patients with CLL (CSLL-C).
[c] Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.
[e] See Discussion for further information on oral fludarabine.
[f] Long and short response cannot be rigorously defined based on available data. A major factor is that the definition would be influenced by the prior treatment. Clinicians will need to use clinical judgement. For instance, after a regimen such as FCR, 3 years may be a reasonable cutoff based on the data from MDACC. However, after chlorambucil, 18-24 months may be a reasonable cutoff.

[g] See Special Considerations for Use of B-Cell Receptor Inhibitors (Ibrutinib and Idelalisib) (NHODG-E).
[h] Indicated for patients for whom rituximab monotherapy would be considered appropriate due to the presence of other co-morbidities (reduced renal function as measured by creatinine clearance <60 mL/min, or NCI CTCAE Grade ≥3 neutropenia or Grade ≥3 thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents.)
[i] Lenalidomide can be given as continuous or intermittent dosing for patients with CLL. Growth factors and/or dose adjustment may be needed to address cytopenias, without necessitating holding treatment. See Badoux XC, Keating MJ, O'Brien SM, et al. Blood 2011;118:Abstract 980. Badoux XC, Keating MJ, Wen S, et al. Blood 2011;118:3489-3498. Chanan-Khan A, Miller KC, Musial L, et al. J Clin Oncol 2006;24:5343-5349.
[j] Less effective for bulky (>5 cm) lymphadenopathy; monitor for CMV reactivation.

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SUGGESTED TREATMENT REGIMENS[a]

CLL with del (17p)

First-line therapy[b] (in alphabetical order)
- Alemtuzumab[c] ± rituximab
- FCR[c,e]
- FR[c,e]
- HDMP + rituximab
- Ibrutinib[g]
- Obinutuzumab + chlorambucil

Relapsed/Refractory therapy[b] (in alphabetical order)
- Alemtuzumab[j] ± rituximab
- RCHOP
- CFAR[c] (cyclophosphamide, fludarabine,[e] alemtuzumab, rituximab)
- HDMP ± rituximab
- Ibrutinib[g]
- Idelalisib + rituximab[g,h]
- Lenalidomide[i] ± rituximab
- Ofatumumab[k]
- OFAR[c,e]

See Supportive Care for
Patients with CLL (**CSLL-C**)

Consider prophylaxis for tumor
lysis syndrome (**See NHODG-B**)

See monoclonal antibody and
viral reactivation (**NHODG-B**)

See Suggested Regimens for CLL without del (11q) or del (17p) (1 of 7)

See Suggested Regimens for CLL with del (11q) (4 of 7)

[a] See references for regimens CSLL-D 6 of 7 and CSLL-D 7 of 7.
[b] See Supportive Care for Patients with CLL (CSLL-C).
[c] Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.
[e] See Discussion for further information on oral fludarabine.
[g] See Special Considerations for Use of B-Cell Receptor Inhibitors (Ibrutinib and Idelalisib) (NHODG-E).
[h] Indicated for patients for whom rituximab monotherapy would be considered appropriate due to the presence of other co-morbidities (reduced renal function as measured by creatinine clearance <60 mL/min, or NCI CTCAE Grade ≥3

neutropenia or Grade ≥3 thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents.)

[i] Lenalidomide can be given as continuous or intermittent dosing for patients with CLL. Growth factors and/or dose adjustment may be needed to address cytopenias, without necessitating holding treatment. See Badoux XC, Keating MJ, O'Brien SM, et al. Blood 2011;118:Abstract 980. Badoux XC, Keating MJ, Wen S, et al. Blood 2011;118:3489-3498. Chanan-Khan A, Miller KC, Musial L, et al. J Clin Oncol 2006;24:5343-5349.

[j] Less effective for bulky (>5 cm) lymphadenopathy; monitor for CMV reactivation.

[k] This is not effective in patients with lymph nodes >5 cm.

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SUGGESTED TREATMENT REGIMENS[a]
(in order of preference)
CLL with del (11q)

First-line therapy[b]

- **Age ≥70 y or younger patients with comorbidities**
  - ➤ **Obinutuzumab + chlorambucil**
  - ➤ **Rituximab + chlorambucil**
  - ➤ **Bendamustine (70 mg/m^2 in cycle 1 with escalation to 90 mg/m^2 if tolerated) ± rituximab**
  - ➤ **Cyclophosphamide, prednisone ± rituximab**
  - ➤ **Reduced-dose FCR[c,d,e]**
  - ➤ **Rituximab**
  - ➤ **Chlorambucil**

- **Age <70 y or older patients without significant comorbidities**
  - ➤ **Chemoimmunotherapy**
    - ◇ **FCR[c,e]**
    - ◇ **Bendamustine ± rituximab**
    - ◇ **PCR**
    - ◇ **Obinutuzumab + chlorambucil**

Relapsed/Refractory therapy[b]

See Suggested Regimens for Relapsed/Refractory therapy for CLL with del (11q) (5 of 7)

See Supportive Care for Patients with CLL (**CSLL-C**)

Consider prophylaxis for tumor lysis syndrome (**See NHODG-B**)

See monoclonal antibody and viral reactivation (**NHODG-B**)

See Suggested Regimens for CLL without del (11q) or del (17p) (1 of 7)
See Suggested Regimens for CLL with del (17p) (3 of 7)

[a] See references for regimens CSLL-D 6 of 7 and CSLL-D 7 of 7.
[b] See Supportive Care for Patients with CLL (CSLL-C).
[c] Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.
[d] In patients ≥70 y, fludarabine does not appear to have a benefit for first-line therapy over other therapies including chlorambucil.
[e] See Discussion for further information on oral fludarabine.

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SUGGESTED TREATMENT REGIMENS[a]
(in order of preference)
CLL with del (11q)
Relapsed/Refractory therapy[b]

- **Long response[f]**
  - ➤ **Retreat as in first-line therapy until short response**

See Supportive Care for Patients with CLL (**CSLL-C**)

Consider prophylaxis for tumor lysis syndrome (**See NHODG-B**)

See monoclonal antibody and viral reactivation (**NHODG-B**)

- **Short response[f] for age ≥70 y (repeating therapy used in immediate prior line not recommended)**
  - ➤ **Ibrutinib[g]**
  - ➤ **Idelalisib + rituximab[g,h]**
  - ➤ **Chemoimmunotherapy**
    - ◇ **Reduced-dose FCR[c,e]**
    - ◇ **Reduced-dose PCR**
    - ◇ **Bendamustine ± rituximab**
    - ◇ **HDMP + rituximab**
    - ◇ **Rituximab + chlorambucil**
  - ➤ **Ofatumumab**
  - ➤ **Lenalidomide[i] ± rituximab**
  - ➤ **Alemtuzumab[j] ± rituximab**
  - ➤ **Dose-dense rituximab (category 2B)**

- **Short response[f] for age <70 y or older patients without significant comorbidities (repeating therapy used in immediate prior line not recommended)**
  - ➤ **Ibrutinib[g]**
  - ➤ **Idelalisib + rituximab[g,h]**
  - ➤ **Chemoimmunotherapy**
    - ◇ **FCR[c,e]**
    - ◇ **PCR**
    - ◇ **Bendamustine ± rituximab**
    - ◇ **Fludarabine[c,e] + alemtuzumab**
    - ◇ **RCHOP**
    - ◇ **OFAR[c,e]**
  - ➤ **Ofatumumab**
  - ➤ **Lenalidomide[i] ± rituximab**
  - ➤ **Alemtuzumab[j] ± rituximab**
  - ➤ **HDMP + rituximab**

See Suggested Regimens for CLL without del (11q) or del (17p) (1 of 7)
See Suggested Regimens for CLL with del (17p) (3 of 7)

[a] See references for regimens CSLL-D 6 of 7 and CSLL-D 7 of 7.
[b] See Supportive Care for Patients with CLL (CSLL-C).
[c] Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.
[e] See Discussion for further information on oral fludarabine.
[f] Long and short response cannot be rigorously defined based on available data. A major factor is that the definition would be influenced by the prior treatment. Clinicians will need to use clinical judgement. For instance, after a regimen such as FCR, 3 years may be a reasonable cutoff based on the data from MDACC. However, after chlorambucil, 18-24 months may be a reasonable cutoff.

[g] See Special Considerations for Use of B-Cell Receptor Inhibitors (Ibrutinib and Idelalisib) (NHODG-E).
[h] Indicated for patients for whom rituximab monotherapy would be considered appropriate due to the presence of other co-morbidities (reduced renal function as measured by creatinine clearance <60 mL/min, or NCI CTCAE Grade ≥3 neutropenia or Grade ≥3 thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents.)
[i] Lenalidomide can be given as continuous or intermittent dosing for patients with CLL. Growth factors and/or dose adjustment may be needed to address cytopenias, without necessitating holding treatment. See Badoux XC, Keating MJ, O'Brien SM, et al. Blood 2011;118:Abstract 980. Badoux XC, Keating MJ, Wen S, et al. Blood 2011;118:3489-3498. Chanan-Khan A, Miller KC, Musial L, et al. J Clin Oncol 2006;24:5343-5349.
[j] Less effective for bulky (>5 cm) lymphadenopathy; monitor for CMV reactivation.

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SUGGESTED TREATMENT REGIMENS
REFERENCES

Alemtuzumab

Lozanski G, Heerema NA, Flinn IW, et al. Alemtuzumab is an effective therapy for chronic lymphocytic leukemia with p53 mutations and deletions. Blood 2004;103:3278-3281.

Keating MJ, Flinn I, Jain V, et al. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: Results of a large international study. Blood 2002;99:3554-3561.

Hillmen P, Skotnicki AB, Robak T, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. J Clin Oncol 2007;25:5616-5623.

Alemtuzumab + rituximab

Faderl S, Thomas DA, O'Brien S, et al. Experience with alemtuzumab plus rituximab in patients with relapsed and refractory lymphoid malignancies. Blood 2003;101:3413-3415.

Bendamustine + rituximab

Fischer K, Cramer P, Busch R et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: A multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol 2011;29:3559-3566.

Fischer K, Cramer P, Busch R, et al. Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: A multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol 2012;30:3209-3216.

Knauf WU, Lissichkov T, Aldaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol 2009;27:4378-4384.

Knauf WU, Lissitchkov T, Aldaoud A, et al. Bendamustine in the treatment of chronic lymphocytic leukemia -consistent superiority over chlorambucil in elderly patients and across clinically defined risk groups [abstract]. Blood 2009;114: Abstract 2367.

Chlorambucil

Eichhorst BF, Busch R, Stilgenbauer S, et al. First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. Blood 2009;114:3382-3391.

Rai KR, Peterson BL, Appelbaum FR, et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. N Engl J Med 2000; 343:1750-1757.

Chlorambucil + rituximab

Hillmen P, Gribben JG, Follows GA, et al. Rituximab plus chlorambucil (R-Chlorambucil) as first-line treatment for chronic lymphocytic leukaemia (CLL): Final analysis of an open-label phase II study [abstract]. Ann Oncol 2011;22:Abstract 120.

Foa R, Alietti A, Guarini A, et al. A phase II study of chlorambucil rituximab (CLB-R) followed by R maintenance vs observation in elderly patients with previously untreated chronic lymphocytic leukemia (CLL): Induction phase results [abstract]. Haematologica 2011;96:Abstract 532.

CFAR (cyclophosphamide, fludarabine, alemtuzumab, rituximab)

Wierda WG, O'Brien S, Ferrajoli A, et al. Combined cyclophosphamide, fludarabine, alemtuzumab, and rituximab (CFAR), an active frontline regimen for high-risk patients with CLL [abstracts]. Blood 2007;110:Abstract 628.

Badoux XC, Keating MJ, Wang X, et al. Cyclophosphamide, fludarabine, rituximab and alemtuzumab (CFAR) as salvage therapy for heavily pre-treated patients with chronic lymphocytic leukemia. Blood 2011;118:2085-2093.

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)

Leporrier M, Chevret S, Cazin B, et al. Randomized comparison of fludarabine, CAP, and CHOP in 938 previously untreated stage B and C chronic lymphocytic leukemia patients. Blood 2001;98:2319-2325.

FCR (fludarabine, cyclophosphamide, rituximab)

Keating MJ, O'Brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. J Clin Oncol 2005;23:4079-4088.

Wierda W, O'Brien S, Wen S, et al. Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab for relapsed and refractory chronic lymphocytic leukemia. J Clin Oncol 2005;23:4070-4078.

Tam CS, O'Brien S, Wierda W, et al. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. Blood 2008;112:975-980.

Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: A randomised, open-label, phase 3 trial. Lancet 2010;376:1164-1174.

Robak T, Dmoszynska A, Solal-Celigny P, et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. J Clin Oncol 2010;28:1756-1765.

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SUGGESTED TREATMENT REGIMENS
REFERENCES

Fludarabine + alemtuzumab
Elter T, Borchmann P, Schulz H, et al. Fludarabine in combination with alemtuzumab is effective and feasible in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: Results of a Phase II trial. J Clin Oncol 2005;23:7024-7031.
Elter T, Gercheva-Kyuchukova L, Pylylpenko H, et al. Fludarabine plus alemtuzumab versus fludarabine alone in patients with previously treated chronic lymphocytic leukaemia: a randomised phase 3 trial. Lancet Oncol 2011;12:1204-1213.
Fludarabine + rituximab
Byrd JC, Peterson BL, Morrison VA, et al. Randomized phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukemia: results from Cancer and Leukemia Group B 9712 (CALGB 9712). Blood 2003;101:6-14.
HDMP (high-dose methylprenisolone) + rituximab
Bowen DA, Call TG, Jenkins GD, et al. Methylprednisolone-rituximab is an effective salvage therapy for patients with relapsed chronic lymphocytic leukemia including those with unfavorable cytogenetic features. Leukemia and Lymphoma 2007;48:2412-2417.
Castro JE, James DF, Sandoval-Sus JD, et al. Rituximab in combination with high-dose methylprednisolone for the treatment of chronic lymphocytic leukemia. Leukemia 2009;23:1779-1789.
Thornton PD, Matutes E, Bosanquet AG, et al. High dose methylprednisolone can induce remissions in CLL patients with p53 abnormalities. Ann Hematol 2003;82:759-765.
Ibrutinib
Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Eng J Med 2013;369:32-42.
Idelalisib
Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N Eng J Med 2014;370:997-1007.
Gopal A, Kahl B, De Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med 2014; 370:1008-1018.
Lenalidomide
Chanan-Khan A, Miller KC, Musial L, et al. Clinical efficacy of lenalidomide in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase II study. J Clin Oncol 2006;24:5343-5349.
Ferrajoli A, Lee BN, Schlette EJ, et al. Lenalidomide induces complete and partial

remissions in patients with relapsed and refractory chronic lymphocytic leukemia. Blood 2008;111:5291-5297.
Badoux XC, Keating MJ, Wen S, et al. Phase II study of lenalidomide and rituximab as salvage therapy for patients with relapsed or refractory chronic lymphocytic leukemia. J Clin Oncol 2013;31:584-591.

Obinutuzumab + chlorambucil
Goede V, Fischer K, Humphrey K,et al, Obinutuzumab (GA101) plus chlorambucil (Clb) or rituximab (R) plus Clb versus Clb alone in patients with chronic lymphocytic leukemia (CLL) and preexisting medical conditions (comorbidities): Final stage 1 results of the CLL11 (BO21004) phase III trial [abstract]. J Clin Oncol 2013;31:Absract 7004.
Ofatumumab
Wierda WG, Kipps TJ, Mayer J, et al. Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol 2010;28:1749-1755.
Coiffier B, Lepretre S, Pedersen LM, et al. Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: a phase 1-2 study. Blood 2008;111:1094-1100.
OFAR (oxaliplatin, fludarabine, cytarabine, rituximab)
Tsimberidou AM, Wierda WG, Plunkett W, et al. Phase I-II study of oxaliplatin, fludarabine, cytarabine, and rituximab combination therapy in patients with Richter's Syndrome or fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol 2008;26:196-203.
Tsimberidou AM, Wierda WG, Badoux X, et al. Evaluation of oxaliplatin, fludarabine, cytarabine, and rituximab (OFAR) combination therapy in aggressive chronic lymphocytic leukemia (CLL) and Richter's syndrome (RS) [abstract]. J Clin Oncol 2010;28: Abstract 6521.
PCR (pentostatin, cyclophosphamide, rituximab)
Lamanna N, Kalaycio M, Maslak P, et al. Pentostatin, cyclophosphamide, and rituximab is an active, well-tolerated regimen for patients with previously treated chronic lymphocytic leukemia. J Clin Oncol 2006;24:1575-1581.
Kay NE, Geyer SM, Call TG, et al. Combination chemoimmunotherapy with pentostatin, cyclophosphamide, and rituximab shows significant clinical activity with low accompanying toxicity in previously untreated B chronic lymphocytic leukemia. Blood 2007;109:405-411.

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RESPONSE DEFINITION AFTER TREATMENT FOR CLL[a,b]

Parameter	Complete Response	Partial Response	Progressive Disease
Group A **Lymphadenopathy†**	**None >1.5 cm**	**Decrease ≥50%**	**Increase ≥50%**
Hepatomegaly	**None**	**Decrease ≥50%**	**Increase ≥50%**
Splenomegaly	**None**	**Decrease ≥50%**	**Increase ≥50%**
Marrow‡	**Normocellular, <30% lymphocytes, no B-lymphoid nodules; hypocellular marrow defines CR with incomplete marrow recovery (CRi)**	**50% reduction in marrow infiltrate, or B-lymphoid nodules**	
Blood lymphocytes	**<4000/µL**	**Decrease ≥50% over baseline**	**Increase ≥50% over baseline**
Group B **Platelet count without growth factors**	**>100,000/µL**	**>100,000/µL or increase ≥50% over baseline**	**Decrease ≥50% over baseline secondary to CLL**
Hemoglobin without transfusions or growth factors	**>11.0 g/dL**	**>11 g/dL or increase ≥50% over baseline**	**Decrease of >2 g/dL from baseline secondary to CLL**
Neutrophils without growth factors‡	**>1500/µL**	**>1500/µL or >50% improvement over baseline**	

Group A criteria define the tumor load. Group B criteria define the function of the hematopoietic system (or marrow).
Complete remission (CR): all of the criteria have to be met, and patients have to lack disease-related constitutional symptoms;
Partial remission (PR): at least two of the criteria of group A plus one of the criteria of group B have to be met;
Stable disease is absence of progressive disease (PD) and failure to achieve at least a PR;
PD: appearance of any new lesions; at least one of the above criteria of group A or group B has to be met.
†Sum of the products of multiple lymph nodes (as evaluated by CT scans in clinical trials, or by physical examination in general practice).
‡These parameters are irrelevant for some response categories.
[a]Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: A report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008;111:5446-5456.
[b]Isolated progressive lymphocytosis in the setting of reduced lymph node size or organomegaly or improvement in hemoglobin/platelets will not be considered progressive disease.

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Follicular Lymphoma[a] (grade 1-2)

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DIAGNOSIS[b]

ESSENTIAL:
- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IGHV and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis. Histologic grading cannot be performed on an FNA.
- Adequate immunophenotyping to establish diagnosis[c,d]
  - IHC panel: CD20, CD3, CD5, CD10, BCL2,[e] BCL6, cyclin D1, CD21, or CD23, or
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- Molecular analysis to detect: antigen gene receptor rearrangements; *BCL2* rearrangements[e]
- Cytogenetics or FISH: t(14;18); *BCL6* rearrangements[e]
- IHC panel: Ki-67[f]

See Workup
(FOLL-2)

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[a]Follicular lymphoma, grade 1-2. Follicular lymphoma, grade 3 is an area of controversy. The distinction between follicular grade 3a and 3b has not been shown to have clinical significance to date. Follicular lymphoma, grade 3 is commonly treated according to the NCCN Diffuse Large B-Cell Lymphoma Guideline (BCEL-1). Any area of diffuse large B-cell lymphoma (DLBCL) in a follicular lymphoma of any grade should be diagnosed and treated as a DLBCL.

[b]Germinal center or follicular center cell phenotype type is not equivalent to follicular lymphoma and occurs in Burkitt lymphoma and some DLBCL.

[c]Typical immunophenotype: CD10+, BCL2+, CD23+/-, CD43-, CD5-, CD20+, cyclin D1, BCL6+. Rare cases of follicular lymphoma may be CD10- or BCL2-.

[d]See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).

[e]In young patients with localized disease that lack BCL2 rearrangement or t(14;18), consider entity of pediatric follicular lymphoma. Analysis of BCL6 rearrangement may be useful for evaluating the diagnosis of pediatric FL.

[f]There are reports showing that Ki-67 proliferation fraction of >30 % may be associated with a more aggressive clinical behavior, but there is no evidence that this should guide treatment decisions.

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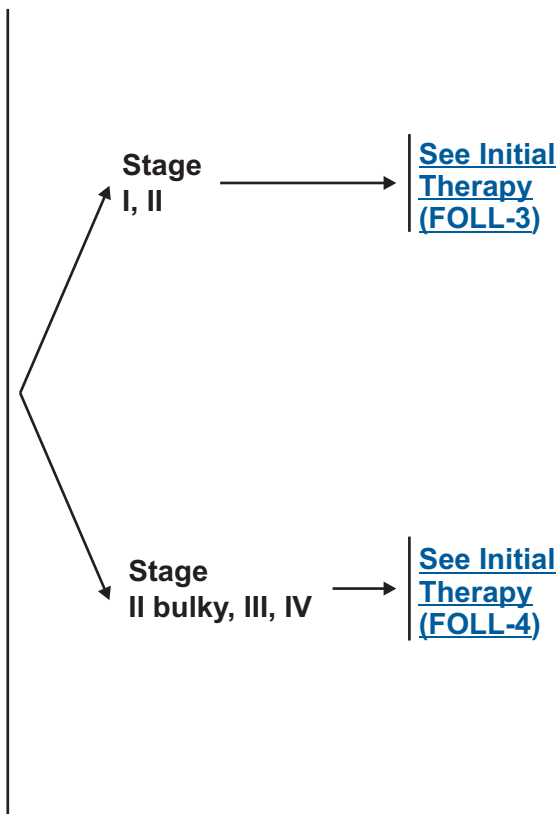
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Follicular Lymphoma[a] (grade 1-2)

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WORKUP

ESSENTIAL:
- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC, differential, platelets
- LDH
- Beta-2-microglobulin
- Comprehensive metabolic panel
- Hepatitis B testing[g]
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Bone marrow biopsy + aspirate to document clinical stage I-II disease[h]
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

USEFUL IN SELECTED CASES:
- MUGA scan/echocardiogram if anthracycline or anthracenedione-based regimen is indicated
- Neck CT
- PET-CT scan
- Uric acid
- Discussion of fertility issues and sperm banking
- SPEP and/or quantitative immunoglobulin levels
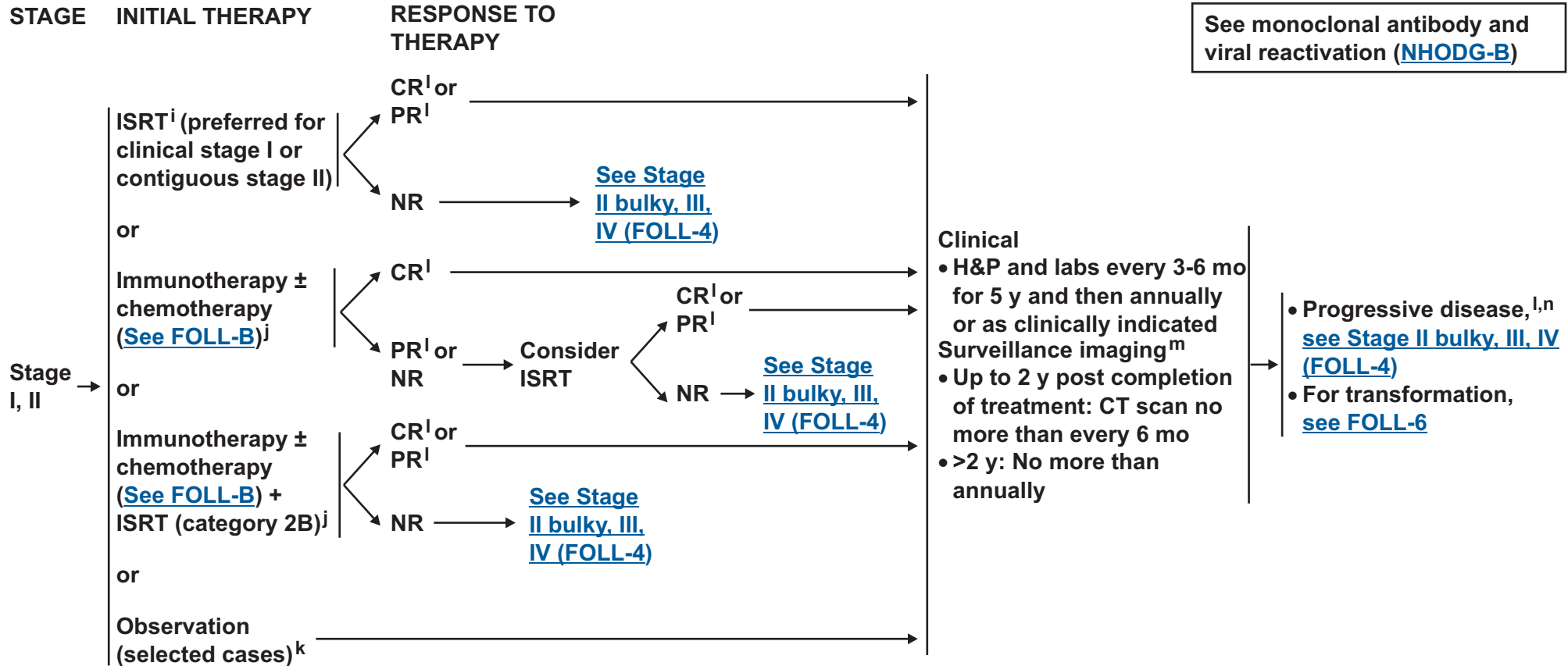- Hepatitis C testing

Stage I, II → **See Initial Therapy (FOLL-3)**

Stage II bulky, III, IV → **See Initial Therapy (FOLL-4)**

[a] Follicular lymphoma, grade 1-2. Follicular lymphoma, grade 3 is an area of controversy. The distinction between follicular grade 3a and 3b has not been shown to have clinical significance to date. Follicular lymphoma, grade 3 is commonly treated according to the NCCN Diffuse Large B-Cell Lymphoma Guideline (BCEL-1). Any area of diffuse large B-cell lymphoma (DLBCL) in a follicular lymphoma of any grade should be diagnosed and treated as a DLBCL.

[g] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

[h] Bilateral or unilateral provided core biopsy is >1.6 cm. If radioimmunotherapy is considered, bilateral cores are recommended and the pathologist should provide the percent of overall cellular elements and the percent of cellular elements involved in the marrow. If observation is initial therapy, bone marrow biopsy may be deferred.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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See monoclonal antibody and viral reactivation (NHODG-B)

STAGE   **INITIAL THERAPY**   **RESPONSE TO THERAPY**

Stage I, II

ISRT[i] (preferred for clinical stage I or contiguous stage II)

or

Immunotherapy ± chemotherapy (See FOLL-B)[j]

or

Immunotherapy ± chemotherapy (See FOLL-B) + ISRT (category 2B)[j]

or

Observation (selected cases)[k]

- CR[l] or PR[l]
- NR → See Stage II bulky, III, IV (FOLL-4)

- CR[l]
- PR[l] or NR → Consider ISRT → CR[l] or PR[l]
  - NR → See Stage II bulky, III, IV (FOLL-4)

- CR[l] or PR[l]
- NR → See Stage II bulky, III, IV (FOLL-4)

Clinical
- H&P and labs every 3-6 mo for 5 y and then annually or as clinically indicated
Surveillance imaging[m]
- Up to 2 y post completion of treatment: CT scan no more than every 6 mo
- >2 y: No more than annually

- **Progressive disease,**[l,n] see Stage II bulky, III, IV (FOLL-4)
- **For transformation,** see FOLL-6

---

[i] See Principles of Radiation Therapy (NHODG-D).

[j] Initiation of chemotherapy or more extended RT can improve FFS (failure-free survival), but has not been shown to improve overall survival. These are options for therapy.

[k] Observation may be appropriate in circumstances where potential toxicity of involved-site RT (ISRT) outweighs potential clinical benefit.
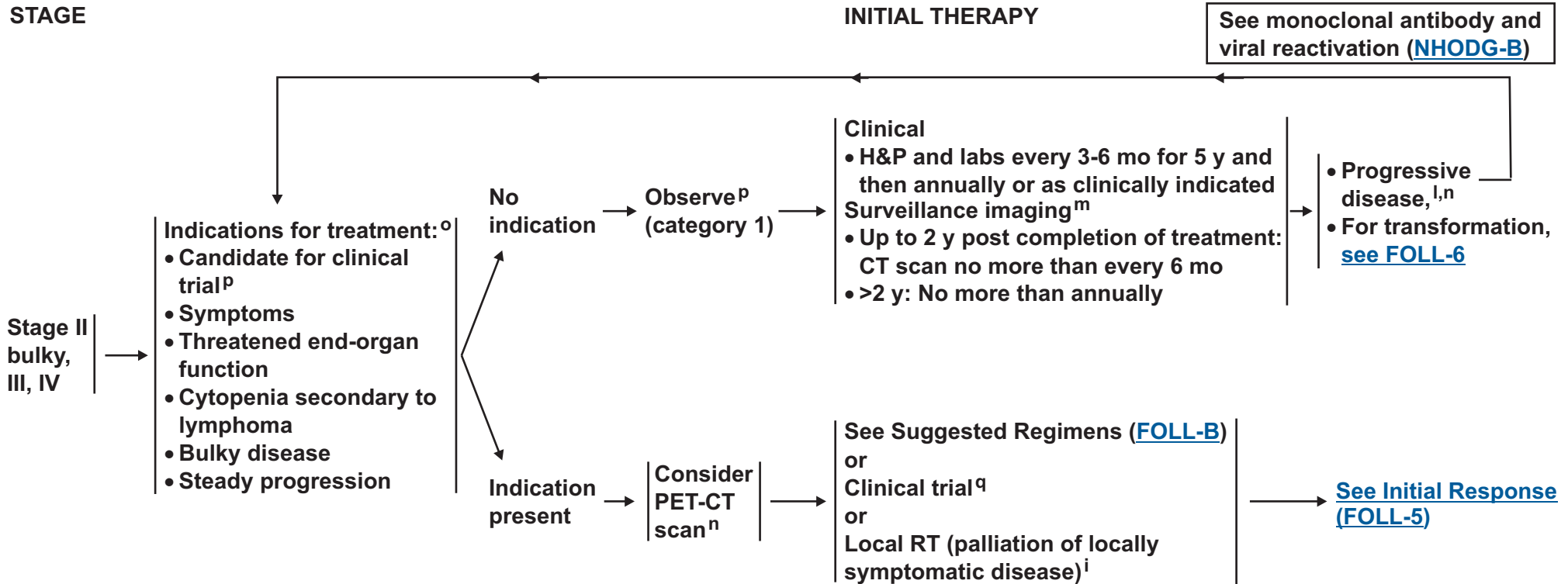
[l] See Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).

[m] Imaging should be performed whenever there are clinical indications. For surveillance imaging, see Discussion for consensus imaging recommendations.

[n] Consider possibility of histologic transformation in patients with progressive disease, especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, or there are new B symptoms. If clinical suspicion of transformation, FDG-PET may help identify areas suspicious for transformation. FDG-PET scan demonstrating marked heterogeneity or sites of intense FDG avidity may indicate transformation, and biopsy should be directed biopsy at the most FDG avid area. Functional imaging does not replace biopsy to diagnose transformation. If transformation is histologically confirmed, treat with anthracycline-based therapy. See Management of Transformation (FOLL-6).
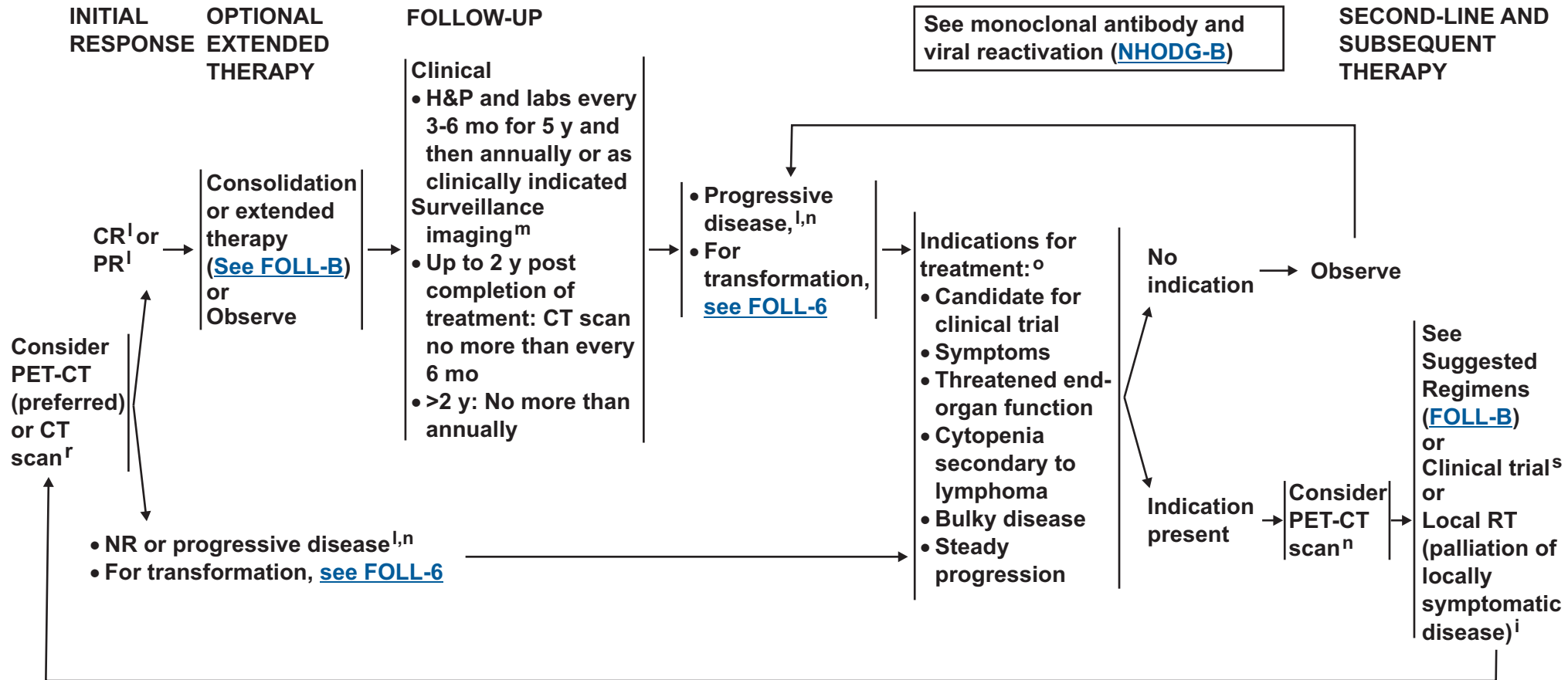

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STAGE   **INITIAL THERAPY**

See monoclonal antibody and
viral reactivation (NHODG-B)

Stage II bulky, III, IV → **Indications for treatment:[o]**
- **Candidate for clinical trial[p]**
- **Symptoms**
- **Threatened end-organ function**
- **Cytopenia secondary to lymphoma**
- **Bulky disease**
- **Steady progression**

No indication → **Observe[p] (category 1)** →

Clinical
- **H&P and labs every 3-6 mo for 5 y and then annually or as clinically indicated**
Surveillance imaging[m]
- **Up to 2 y post completion of treatment: CT scan no more than every 6 mo**
- **>2 y: No more than annually**

- **Progressive disease,[l,n]**
- **For transformation, see FOLL-6**

Indication present → **Consider PET-CT scan[n]** →

See Suggested Regimens (FOLL-B)
or
Clinical trial[q]
or
Local RT (palliation of locally symptomatic disease)[i]

→ **See Initial Response (FOLL-5)**

---

[i]See Principles of Radiation Therapy (NHODG-D).

[l]See Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).

[m]Imaging should be performed whenever there are clinical indications. For surveillance imaging, see Discussion for consensus imaging recommendations.

[n]Consider possibility of histologic transformation in patients with progressive disease, especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, or there are new B symptoms. If clinical suspicion of transformation, FDG-PET may help identify areas suspicious for transformation. FDG-PET scan demonstrating marked heterogeneity or sites of intense FDG avidity may indicate transformation, and biopsy should be directed biopsy at the most FDG avid area. Functional imaging does not replace biopsy to diagnose transformation. If transformation is histologically confirmed, treat with anthracycline-based therapy. See Management of Transformation (FOLL-6).
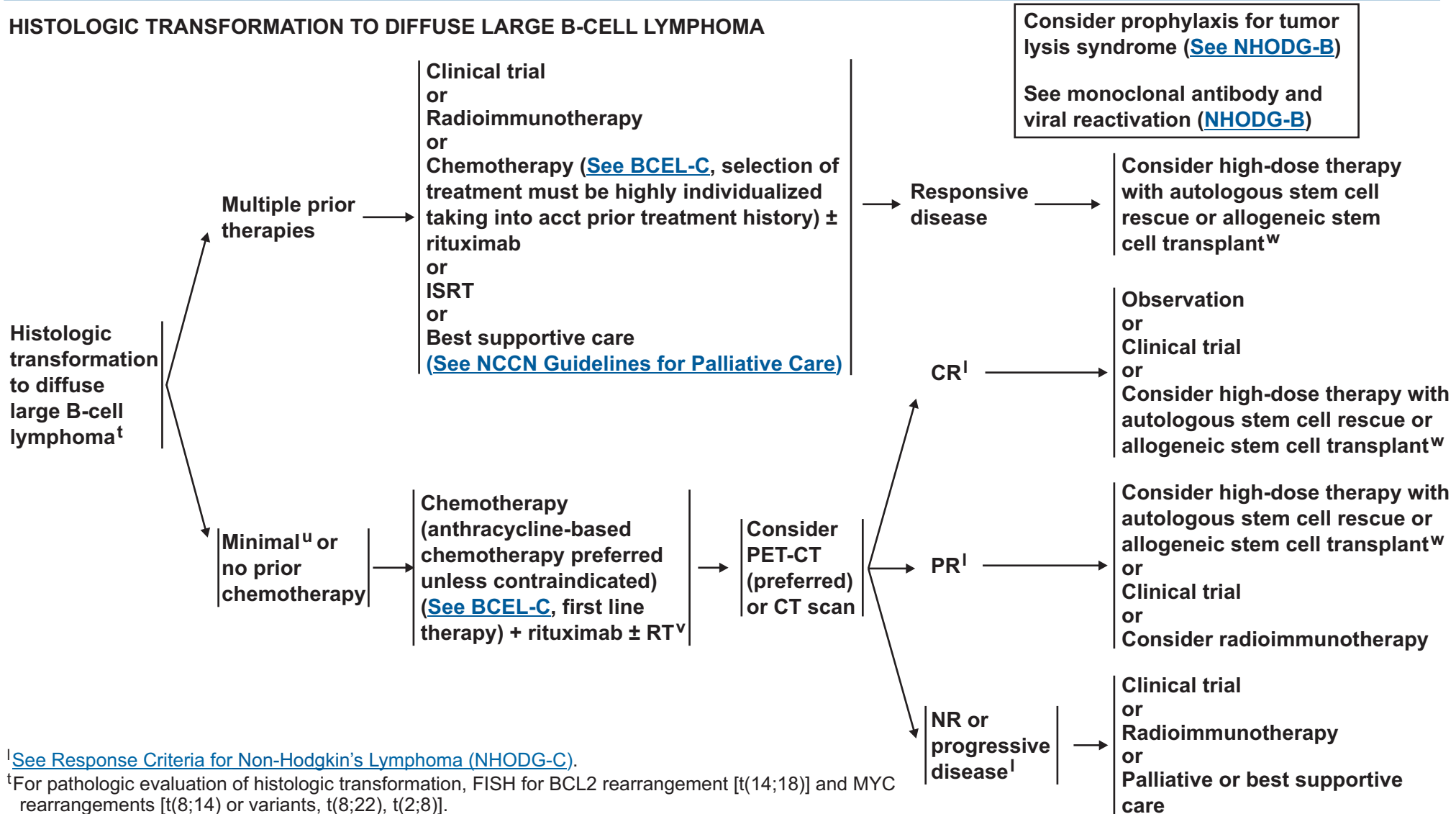
[o]See GELF criteria (FOLL-A).

[p]Consider clinical trials appropriate for patients on observation.

[q]Given incurability with conventional therapy, consider investigational therapy as first line of treatment.

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INITIAL RESPONSE

OPTIONAL EXTENDED THERAPY

FOLLOW-UP

See monoclonal antibody and viral reactivation (NHODG-B)

SECOND-LINE AND SUBSEQUENT THERAPY

CR[l] or PR[l] →

Consider PET-CT (preferred) or CT scan[r]

Consolidation or extended therapy (See FOLL-B) or Observe →

Clinical
- H&P and labs every 3-6 mo for 5 y and then annually or as clinically indicated

Surveillance imaging[m]
- Up to 2 y post completion of treatment: CT scan no more than every 6 mo
- >2 y: No more than annually

→

- Progressive disease,[l,n]
- For transformation, see FOLL-6

→

Indications for treatment:[o]
- Candidate for clinical trial
- Symptoms
- Threatened end-organ function
- Cytopenia secondary to lymphoma
- Bulky disease
- Steady progression

No indication → Observe

Indication present → Consider PET-CT scan[n] →

See Suggested Regimens (FOLL-B) or Clinical trial[s] or Local RT (palliation of locally symptomatic disease)[i]

- NR or progressive disease[l,n]
- For transformation, see FOLL-6

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[i] See Principles of Radiation Therapy (NHODG-D).

[l] See Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).

[m] Imaging should be performed whenever there are clinical indications. For surveillance imaging, see Discussion for consensus imaging recommendations.

[n] Consider possibility of histologic transformation in patients with progressive disease, especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, or there are new B symptoms. If clinical suspicion of transformation, FDG-PET may help identify areas suspicious for transformation. FDG-PET scan demonstrating marked heterogeneity or sites of intense FDG avidity may indicate transformation and biopsy should be directed biopsy at the most FDG avid area. Functional imaging does not replace biopsy to diagnose transformation. If transformation is histologically confirmed, treat with anthracycline-based therapy. See Management of Transformation (FOLL-6).

[o] See GELF criteria (FOLL-A).

[r] A PET-positive PR is associated with a shortened PFS (See Discussion); however, additional treatment at this juncture has not been shown to change outcome.

[s] Clinical trials may involve novel agents, regimens, or transplantation.

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HISTOLOGIC TRANSFORMATION TO DIFFUSE LARGE B-CELL LYMPHOMA

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

Histologic transformation to diffuse large B-cell lymphoma[t]

Multiple prior therapies →
Clinical trial
or
Radioimmunotherapy
or
Chemotherapy (See BCEL-C, selection of treatment must be highly individualized taking into acct prior treatment history) ± rituximab
or
ISRT
or
Best supportive care
(See NCCN Guidelines for Palliative Care)
→ **Responsive disease** → Consider high-dose therapy with autologous stem cell rescue or allogeneic stem cell transplant[w]

Minimal[u] or no prior chemotherapy →
Chemotherapy (anthracycline-based chemotherapy preferred unless contraindicated) (See BCEL-C, first line therapy) + rituximab ± RT[v]
→ Consider PET-CT (preferred) or CT scan →

CR[l] → Observation
or
Clinical trial
or
Consider high-dose therapy with autologous stem cell rescue or allogeneic stem cell transplant[w]

PR[l] → Consider high-dose therapy with autologous stem cell rescue or allogeneic stem cell transplant[w]
or
Clinical trial
or
Consider radioimmunotherapy

NR or progressive disease[l] → Clinical trial
or
Radioimmunotherapy
or
Palliative or best supportive care

[l]See Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[t]For pathologic evaluation of histologic transformation, FISH for BCL2 rearrangement [t(14;18)] and MYC rearrangements [t(8;14) or variants, t(8;22), t(2;8)].
[u]Involved-site RT alone or one course of single-agent therapy including rituximab.
[v]If locoregional transformation, consider adding RT.
[w]Strongly recommend this treatment be given in the context of a clinical trial.

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GELF CRITERIA [a,b]

- **Involvement of ≥3 nodal sites, each with a diameter of ≥3 cm**
- **Any nodal or extranodal tumor mass with a diameter of ≥7 cm**
- **B symptoms**
- **Splenomegaly**
- **Pleural effusions or peritoneal ascites**
- **Cytopenias (leukocytes <1.0 x 10^9/L and/or platelets <100 x 10^9/L)**
- **Leukemia (>5.0 x 10^9/L malignant cells)**

FLIPI - 1 CRITERIA [a,c,d]

Age	**≥60 y**
Ann Arbor stage	**III-IV**
Hemoglobin level	**<12 g/dL**
Serum LDH level	**>ULN (upper limit of normal)**
Number of nodal sites [d]	**≥5**

Risk group according to FLIPI chart

	Number of factors
Low	**0-1**
Intermediate	**2**
High	**≥3**

Nodal Areas

Right Cervical
Preauricular
Upper Cervical
Median or Lower
Postcervical
Supraclavicular

Left Cervical
Preauricular
Upper Cervical
Median or Lower
Postcervical
Supraclavicular

Mediastinal
Paratracheal
Mediastinal
Hilar

Right Axillary

Left Axillary

Right Epitrochlear

Left Epitrochlear

Para-Aortic
Para-Aortic
Common Iliac
External Iliac

Mesenteric
Mesenteric
Splenic Hilar
Portal
Celiac

Right Inguinal
Inguinal
Femoral

Left Inguinal
Inguinal
Femoral

Right Popliteal

Left Popliteal

Legend for labels
Blue = Bilateral
Black = Midline

Mannequin used for counting the number of involved areas.[e]

[a] This provides useful prognostic information that may be used to guide therapeutic decisions.

[b] Solal-Celigny P, Lepage E, Brousse N, et al. Doxorubicin containing regimen with or without interferon alfa 2b for advanced follicular lymphomas: final analysis of survival and toxicity in the Groupe d'Etude des Lymphomes Folliculaire 86 trial. J Clin Oncol 1998;16:2332-2338.

[c] This research was originally published in Blood. Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood 2004;104:1258-1265. (c) the American Society of Hematology.

[d] FLIPI-2 (Federico M, Bellei M, Marcheselli L, et al. J Clin Oncol 2009;27:4555-4562) predicts for outcomes after active therapy, see Discussion.

[e] The map is used to determine the number of nodal sites in FLIPI-1 criteria and is different than the conventional Ann Arbor site map.

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SUGGESTED TREATMENT REGIMENS[a,b]
(in alphabetical order)

First-line Therapy[c]
- Bendamustine + rituximab (category 1)
- RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)
- RCVP (rituximab, cyclophosphamide, vincristine, prednisone) (category 1)
- Rituximab (375 mg/m² weekly for 4 doses)

First-line Therapy for Elderly or Infirm (if none of the above are expected to be tolerable in the opinion of treating physician)
- Radioimmunotherapy[d,e]
- Rituximab (preferred) (375 mg/m² weekly for 4 doses)
- Single-agent alkylators (eg, chlorambucil or cyclophosphamide) ± rituximab

First-line Consolidation or Extended Dosing (optional)[f]
- Radioimmunotherapy (after induction with chemotherapy or chemoimmunotherapy)[d,e,g] (category 1)
- Rituximab maintenance 375 mg/m² one dose every 8 wks for 12 doses for patients initially presenting with high tumor burden (category 1)
- If initially treated with single-agent rituximab, consolidation with rituximab 375 mg/m² one dose every 8 weeks for 4 doses

Second-line and Subsequent Therapy
- Chemoimmunotherapy (as listed under first-line therapy)
- FCMR[h] (fludarabine, cyclophosphamide, mitoxantrone, rituximab) (category 1)
- Fludarabine[h] + rituximab
- Idelalisib[i]
- Lenalidomide ± rituximab
- Radioimmunotherapy[d,e] (category 1)
- Rituximab
- RFND[h,j] (rituximab, fludarabine, mitoxantrone, dexamethasone)
- See Second-line Therapy for DLBCL (BCEL-C 1 of 3) without regard to transplantability

Second-line Consolidation or Extended Dosing
- High-dose therapy with autologous stem cell rescue
- Allogeneic stem cell transplant for highly selected patients
- Rituximab maintenance 375 mg/m² one dose every 12 wks for 2 years (category 1) (optional)

For patients with locally bulky or locally symptomatic disease, consider ISRT 4-30 Gy ± additional systemic therapy.

> Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
> See monoclonal antibody and viral reactivation (NHODG-B)

[a] See references for regimens FOLL-B 2 of 3 and FOLL-B 3 of 3.

[b] The choice of initial therapy requires consideration of many factors, including age, comorbidities, and future treatment possibilities (eg, HDT with SCR). Therefore, treatment selection is highly individualized.

[c] In combination chemotherapy, addition of rituximab has consistently increased overall response rate, response duration, and progression-free survival. In addition, some studies have demonstrated an overall survival benefit.

[d] Selection of patients requires adequate marrow cellularity >15% and <25% involvement of lymphoma in bone marrow, and platelets >100,000. In patients with prior autologous stem cell rescue, referral to a tertiary care center is highly recommended for radioimmunotherapy.

[e] If radioimmunotherapy is considered, bilateral cores are recommended and the pathologist should provide the percent of overall cellular elements and the percent of cellular elements involved in the marrow. Cytogenetics ± FISH for known MDS markers. As of 2010, updates suggest a trend towards an increased risk of MDS with RIT treatment.

[f] First-line consolidation with radioimmunotherapy or extended dosing of rituximab after bendamustine + rituximab has not been studied.

[g] The full impact of an induction regimen containing rituximab on RIT consolidation is unknown.

[h] Fludarabine-containing regimens negatively impact stem cell mobilization for transplant.

[i] See Special Considerations for Use of B-Cell Receptor Inhibitors (Ibrutinib and Idelalisib) (NHODG-E).

[j] RFND regimen may be associated with stem cell toxicity and secondary malignancies (see Discussion).

> Note: All recommendations are category 2A unless otherwise indicated.
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FOLL-B
1 of 3

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SUGGESTED TREATMENT REGIMENS
References

First-line Therapy

Bendamustine + rituximab
Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet 2013;381:1203-1210.

Cyclophosphamide
Peterson BA, Petroni GR, Frizzera G, et al. Prolonged single-agent versus combination chemotherapy in indolent follicular lymphomas: a study of the cancer and leukemia group B. J Clin Oncol 2003;21:5-15.

RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)
Czuczman MS, Weaver R, Alkuzweny B, et al. Prolonged clinical and molecular remission in patients with low-grade or follicular non-Hodgkin's lymphoma treated with rituximab plus CHOP chemotherapy: 9-year follow-up. J Clin Oncol 2004;22:4711-4716.
Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2005;106:3725-3732.

RCVP (rituximab, cyclophosphamide, vincristine, prednisone)
Marcus R, Imrie K, Solal-Celigny P, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J Clin Oncol 2008;26:4579-4586.

Rituximab
Hainsworth JD, Litchy S, Burris HA, III, et al. Rituximab as first-line and maintenance therapy for patients with indolent Non-Hodgkin's lymphoma. J Clin Oncol 2002;20:4261-4267.
Colombat P, Salles G, Brousse N, et al. Rituximab (anti-CD20 monoclonal antibody) as single first-line therapy for patients with follicular lymphoma with a low tumor burden: Clinical and molecular evaluation. Blood 2001;97:101-106.

Radioimmunotherapy
Scholz CW, Pinto A, Linkesch W, et al. 90Yttrium ibritumomab tiuxetan as first line treatment for follicular lymphoma. first results from an international phase II clinical trial [abstract]. Blood 2010;116:Abstract 593.

First-line Consolidation or Extended Dosing

Radioimmunotherapy (after induction with chemotherapy or chemoimmunotherapy)
Morschhauser F, Radford J, Van Hoof A, et al. Phase III trial of consolidation therapy with Yttrium-90–Ibritumomab Tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma. J Clin Oncol 2008;26:5156-5164.
Hagenbeek A, Radford J, Van Hoof A, et al. 90Y-Ibritumomab tiuxetan (Zevalin®) consolidation of first remission in advanced-stage follicular non-hodgkin's lymphoma: Updated results after a median follow-up of 66.2 months from the international, randomized, phase III First-Line Indolent Trial (FIT) in 414 Patients [abstract]. Blood 2010;116:Abstract 594.
Morschhauser F, Radford J, Van Hoof A, et al. 90Yttrium-ibritumomab tuxetan consolidation of first remission in advanced-stage follicular non-Hodgkin lymphoma: Updated results after a median follow-up of 7.3 years from the international, randomized, phase III first-line indolent trial. J Clin Oncol 2013;31:1977-1983.

Chemotherapy followed by rituximab
Salles GA, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): A phase 3, randomised controlled trial. The Lancet 2011;377:42-51.

Extended dosing with rituximab
Ghielmini M, Schmitz SH, Cogliatti SB, et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule. Blood 2004;103:4416-4423.

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SUGGESTED TREATMENT REGIMENS
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Second-line and Subsequent Therapy
FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab)
Forstpointner R, Dreyling M, Repp R, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared to FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas - results of a prospective randomized study of the German low grade lymphoma study group (GLSG). Blood 2004;104:3064-3071.

Fludarabine + rituximab
Czuczman MS, Koryzna A, Mohr A, et al. Rituximab in combination with fludarabine chemotherapy in low-grade of follicular lymphoma. J Clin Oncol 2005;23:694-704.

Idelalisib
Gopal A, Kahl B, De Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med 2014;370:1008-1018.

Lenalidomide ± rituximab
Leonard J, Jung S-H, Johnson JL, et al. CALGB 50401: A randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma [abstract]. J Clin Oncol 2012;30:Abstract 8000.
Witzig TE, Wiernik PH, Moore T, et al. Lenalidomide oral monotherapy produces durable responses in relapsed or refractory indolent non-Hodgkin's Lymphoma. J Clin Oncol 2009;27:5404-5409.

Radioimmunotherapy
Witzig TE, Flinn IW, Gordon LI, et al. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. J Clin Oncol 2002;20:3262-3269.
Witzig TE, Gordon LI, Cabanillas F, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol 2002;20:2453-2463.

Rituximab
McLaughlin P, Grillo-Lopez AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol 1998;16:2825-2833.
Ghielmini M, Schmitz SH, Cogliatti SB, et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule. Blood 2004;103:4416-4423.

RFND (rituximab, fludarabine, mitoxantrone, dexamethasone) + rituximab
McLaughlin P, Hagemeister FB, Rodriguez MA, et al. Safety of fludarabine, mitoxantrone, and dexamethasone combined with rituximab in the treatment of stage IV indolent lymphoma. Semin Oncol 2000;27:37-41.

Second-line Consolidation or Extended Dosing
Rituximab maintenance
van Oers MHJ, Van Glabbeke M, Giurgea L, et al. Rituximab maintenance treatment of relapsed/resistant follicular non-hodgkin's lymphoma: Long-term outcome of the EORTC 20981 Phase III randomized Intergroup Study. J Clin Oncol 2010;28:2853-2858.
Forstpointer R, Unterhalt M, Dreyling M, et al. Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG). Blood 2006;108:4003-4008.

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Marginal Zone Lymphomas

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Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

- Gastric ⟶ **See Diagnosis and Workup (MALT-1)**

- Nongastric/ Noncutaneous ⟶ **See Diagnosis and Workup (NGMLT-1)**

- Cutaneous ⟶ **See Primary Cutaneous Marginal Zone Lymphoma (CUTB-1)**

Nodal marginal zone lymphoma ⟶ **See Diagnosis and Workup (NODE-1)**

Splenic marginal zone lymphoma ⟶ **See Diagnosis and Workup (SPLN-1)**

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Extranodal Marginal Zone B-Cell Lymphoma
Gastric MALT Lymphoma

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DIAGNOSIS

ESSENTIAL:

- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic. [a,b]
- Diagnosis of gastric MALT lymphoma requires an endoscopic biopsy and an FNA is never adequate.
- Adequate immunophenotyping to establish diagnosis [c,d]
  - ➤ IHC Panel: CD20, CD3, CD5, CD10, BCL2, kappa/lambda, CD21 or CD23, cyclin D1, BCL6
    or
  - ➤ Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10
- Helicobacter pylori (H. pylori) stain (gastric), if positive, then PCR or FISH for t(11;18) [e]

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Molecular analysis to detect: antigen receptor gene rearrangements; MYD88 mutation status to differentiate WM versus MZL if plasmacytic differentiation present
- Cytogenetics or FISH: t(1;14); t(3;14); t(11;14); [f] t(11;18)
- FISH or PCR: t(14;18)

WORKUP

ESSENTIAL:

- Physical exam with attention to nongastric sites (eyes, skin)
- Performance status
- CBC, differential, platelets
- Comprehensive metabolic panel
- LDH
- If H. pylori negative by histopathology, then use noninvasive H. pylori testing (stool antigen test, urea breath test, blood antibody test)
- Hepatitis B testing [g] if rituximab contemplated
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

USEFUL IN SELECTED CASES:

- Bone marrow biopsy ± aspirate
- MUGA scan/echocardiogram if anthracycline or anthracenedione-based regimen is indicated
- Endoscopy with ultrasound (if available) with multiple biopsies of anatomical sites [h]
- Hepatitis C testing
- Discussion of fertility issues and sperm banking
- SPEP

See Initial Therapy (MALT-2)

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[a] Nondiagnostic atypical lymphoid infiltrates that are H. Pylori positive should be rebiopsied to confirm or exclude lymphoma prior to treatment of H. Pylori.

[b] Any area of DLBCL should be treated according to the NCCN Guidelines for Diffuse Large B-Cell Lymphoma (BCEL-1).

[c] Typical immunophenotype: CD10-, CD5-, CD20+, cyclin D1-, BCL2 follicles.

[d] See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).

[e] Locally advanced disease is more likely in patients with gastric MALT lymphoma with t(11;18), which is less likely to respond to antibiotics.

[f] If IHC for cyclin D1 is positive, FISH for t(11;14) is not necessary.

[g] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

[h] This is particularly useful for H. pylori-positive cases because the likelihood of tumor response is related to depth of tumor invasion.
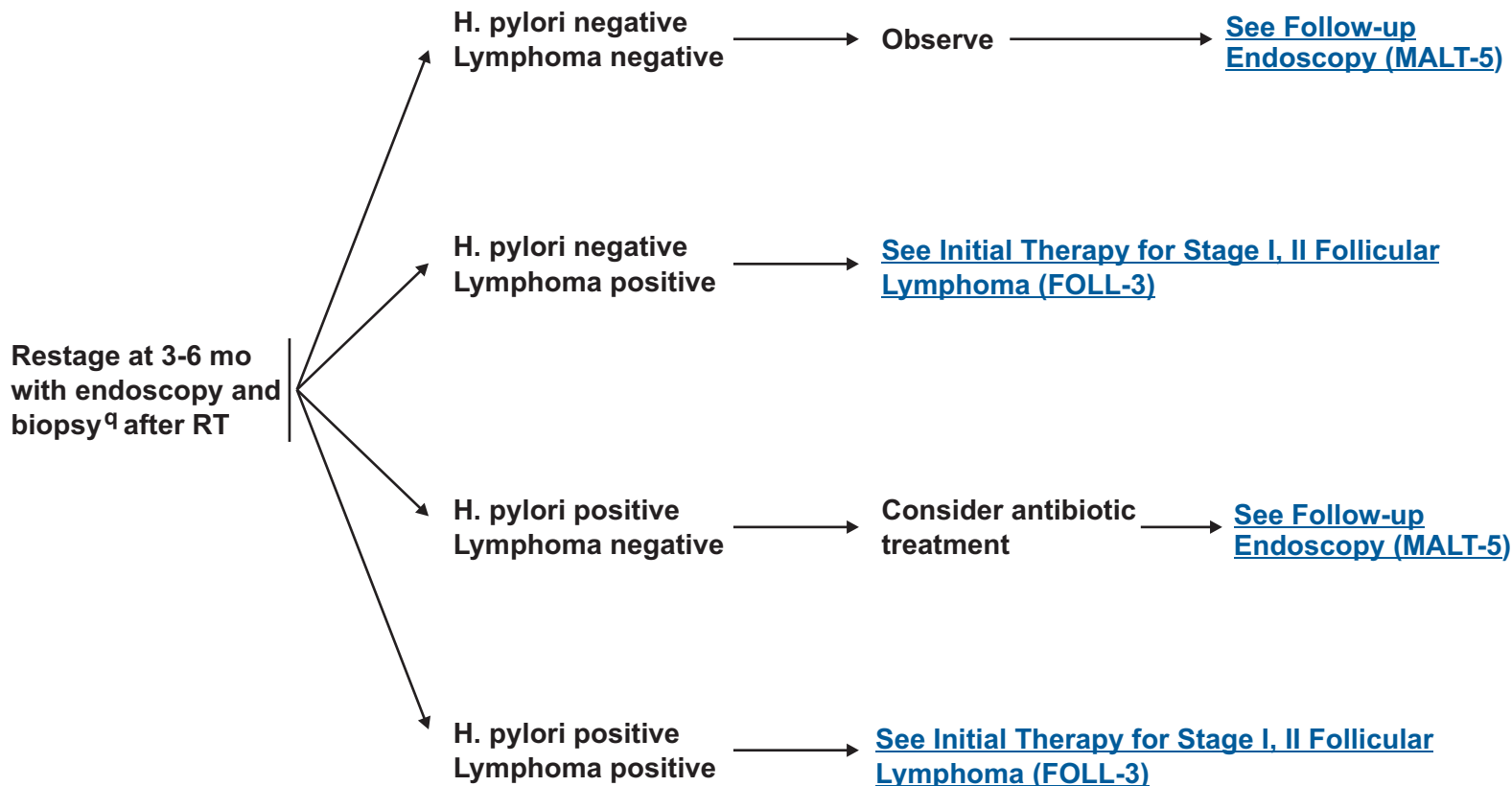

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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Gastric MALT Lymphoma

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STAGE[i] **INITIAL THERAPY**

See monoclonal antibody and viral reactivation (**NHODG-B**)

Stage I_{E1}, H. pylori positive → Currently accepted antibiotic therapy for H. pylori → Evaluate for H. pylori eradication with endoscopy (**MALT-3**)

Stage I_{E2}[j] or Stage II_E[j] H. pylori positive → Currently accepted antibiotic therapy for H. pylori → Evaluate for H. pylori eradication with endoscopy (**MALT-3**)

H. pylori positive, t(11;18) positive[k] → Currently accepted antibiotic therapy to treat H. pylori →

- Asymptomatic → Consider ISRT[l,m] or rituximab (if ISRT is contraindicated) → Endoscopy for restaging, as per **MALT-4**
- Symptomatic →

Stage I_E or II_E H. pylori negative → ISRT[l,m] (preferred) or Rituximab (if ISRT is contraindicated) → Endoscopy for restaging, as per **MALT-4**

Stage III_E/IV (advanced-stage disease uncommon) → Indications for treatment:
- **Candidate for clinical trial[n]**
- **Symptoms**
- **GI bleeding**
- **Threatened end-organ function**
- **Bulky disease**
- **Steady progression**
- **Patient preference**

→ **No indication** → **Observe**

→ **Indication present[o]** → Induction chemo-immunotherapy[p] or Locoregional RT in specific settings[m] → Endoscopy for restaging, if evidence of recurrence, manage per **NCCN Guidelines for Follicular Lymphoma (FOLL-5)**

[i] See Lugano Staging System for Gastrointestinal Lymphomas (**MALT-A**).

[j] Involvement of submucosa or regional lymph nodes are much less likely to respond to antibiotic therapy. If there is persistent disease after evaluation, RT may be considered earlier in the course.

[k] t(11;18) is a predictor for lack of tumor response (<5%) to antibiotics. Antibiotics are used in these patients to eradicate the H. plyori infection. These patients should be considered for alternative therapy of the lymphoma. Liu H, Ye H, Ruskone-Fourmestraux A, et al. t(11;18) is a marker for all stage gastric MALT lymphomas that will not respond to H. pylori eradication. Gastroenterology 2002;122:1286-1294.

[l] If negative by both histology and serum antibodies, RT is recommended.

[m] See Principles of Radiation Therapy (**NHODG-D**).

[n] Given incurability with conventional therapy, consider investigational therapy as first line of treatment.

[o] Surgical resection is generally limited to specific clinical situations (ie, life-threatening hemorrhage).

[p] See Suggested Treatment Regimens (**FOLL-B**).

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3-MONTH RESTAGING AND FOLLOW-UP ENDOSCOPY

AFTER ANTIBIOTICS

ADDITIONAL THERAPY

Restage at 3 mo with endoscopy/biopsy^q for H. pylori/lymphoma (restage earlier than 3 mo if symptomatic) after antibiotics

→ **H. pylori negative, Lymphoma negative** → Observe →

→ **H. pylori negative, Lymphoma positive**
  → Asymptomatic → Observe for another 3 mo^r or RT^{m,r,s}
  → Symptomatic → RT^m →

→ **H. pylori positive, Lymphoma negative** → Second-line antibiotic treatment →

→ **H. pylori positive, Lymphoma positive**
  → Stable disease → Second-line antibiotic treatment →
  → Progressive or symptomatic disease → RT^m and second-line antibiotic treatment

See Follow-up Endoscopy (MALT-5)

^{m}See Principles of Radiation Therapy (NHODG-D).
^{q}Biopsy to rule out large cell lymphoma. Any area of DLBCL should be treated according to the NCCN Guidelines for Diffuse Large B-Cell Lymphoma (BCEL-1).
^{r}If re-evaluation suggests slowly responding disease or asymptomatic nonprogression, continued observation may be warranted. RT can be considered as early as 3 mo after observation but can be prolonged to 18 mo (category 2B).
^{s}If patient originally had clinical Stage I$_{E2}$ or Stage II$_E$, early RT should be considered if there is no response to antibiotics.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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3-6 MONTH RESTAGING AND FOLLOW-UP ENDOSCOPY

AFTER RT   **ADDITIONAL THERAPY**

Restage at 3-6 mo with endoscopy and biopsy[q] after RT

→ H. pylori negative
Lymphoma negative → Observe → **See Follow-up Endoscopy (MALT-5)**

→ H. pylori negative
Lymphoma positive → **See Initial Therapy for Stage I, II Follicular Lymphoma (FOLL-3)**

→ H. pylori positive
Lymphoma negative → Consider antibiotic treatment → **See Follow-up Endoscopy (MALT-5)**

→ H. pylori positive
Lymphoma positive → **See Initial Therapy for Stage I, II Follicular Lymphoma (FOLL-3)**

[q]Biopsy to rule out large cell lymphoma. Any area of DLBCL should be treated according to the NCCN Guidelines for Diffuse Large B-Cell Lymphoma (BCEL-1).

Note: All recommendations are category 2A unless otherwise indicated.
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FOLLOW-UP ENDOSCOPY

Repeat endoscopy after 3 mo[q]

CR → Clinical follow-up every 3-6 mo for 5 y and then yearly or as clinically indicated[t]

→ Recurrence post RT → **See follicular lymphoma indications for treatment (FOLL-4)**

→ Recurrence post antibiotics → Systemic → **See follicular lymphoma indications for treatment (FOLL-4)**

→ Locoregional RT[m]

NR → Previous RT → **See follicular lymphoma indications for treatment (FOLL-4)**

→ Previous antibiotic treatment → Locoregional RT[m]
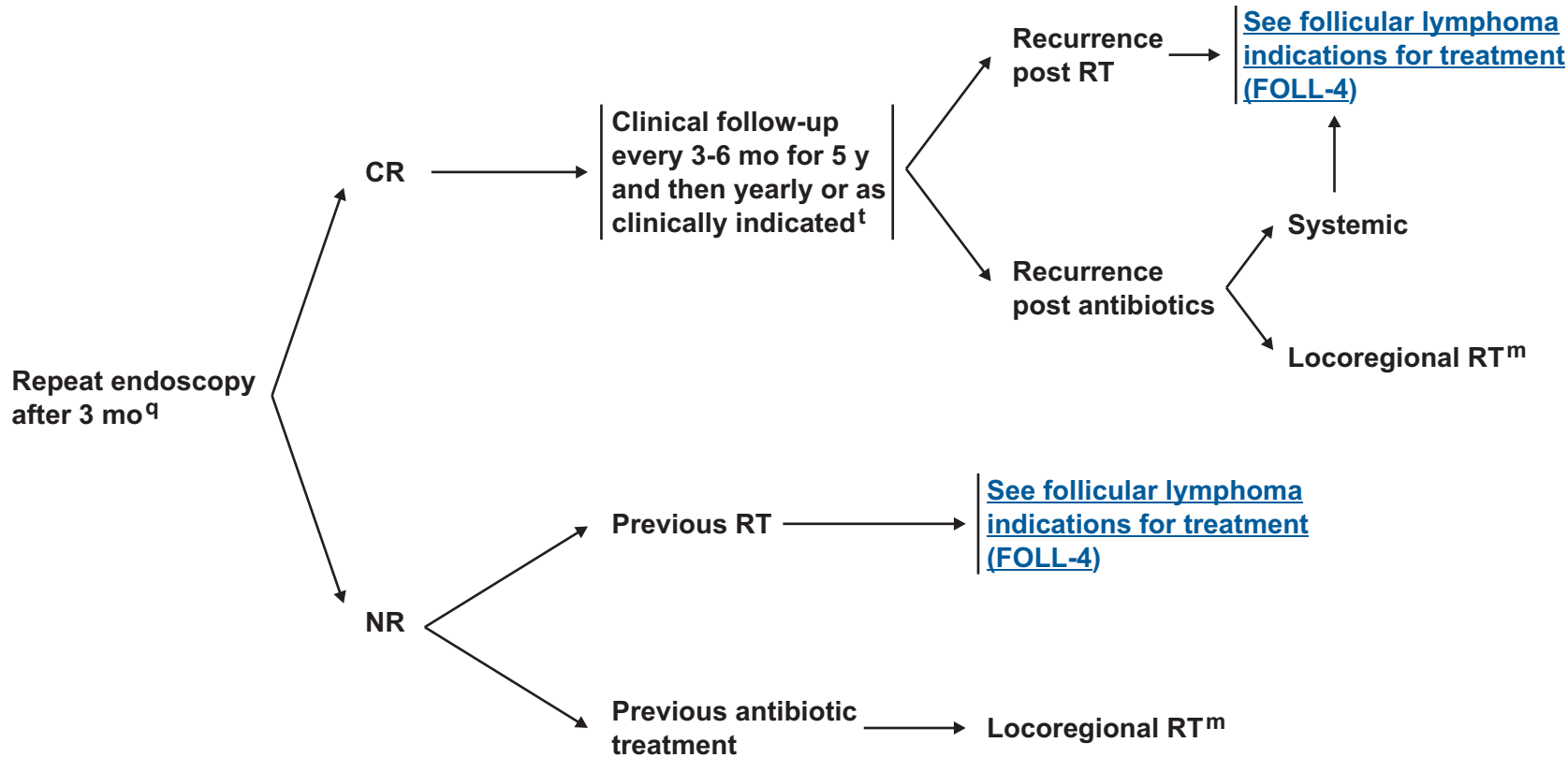
[m]See Principles of Radiation Therapy (NHODG-D).
[q]Biopsy to rule out large cell lymphoma. Any area of DLBCL should be treated according to the NCCN Guidelines for Diffuse Large B-Cell Lymphoma (BCEL-1).
[t]Optimal interval for follow-up endoscopy and imaging is not known. Follow-up endoscopy and imaging at NCCN Member Institutions is driven by symptoms.

Note: All recommendations are category 2A unless otherwise indicated.
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STAGING OF GASTRIC MALT LYMPHOMA: COMPARISON OF DIFFERENT SYSTEMS

Lugano Staging System for Gastrointestinal Lymphomas		Ann Arbor Stage	TNM Staging System Adapted for Gastric Lymphoma	Tumor Extension
Stage I$_E$	**Confined to GI tract**[a]			
	I$_{E1}$ = mucosa, submucosa	I$_E$	T1 N0 M0	Mucosa, submucosa
	I$_{E2}$ = muscularis propria, serosa	I$_E$	T2 N0 M0	Muscularis propria
		I$_E$	T3 N0 M0	Serosa
Stage II$_E$	**Extending into abdomen**			
	II$_{E1}$ = local nodal involvement	II$_E$	T1-3 N1 M0	Perigastric lymph nodes
	II$_{E2}$ = distant nodal involvement	II$_E$	T1-3 N2 M0	More distant regional lymph nodes
Stage II$_E$	**Penetration of serosa to involve adjacent organs or tissues**	II$_E$	T4 N0 M0	Invasion of adjacent structures
Stage IV[b]	**Disseminated extranodal involvement or concomitant supradiaphragmatic nodal involvement**	III$_E$	T1-4 N3 M0	Lymph nodes on both sides of the diaphragm/distant metastases (eg, bone marrow or additional extranodal sites)
		IV	T1-4 N0-3 M1	

Yahalom J et al. Extranodal Marginal Zone B-cell Lymphoma of Mucosa-Associated Lymphoid Tissue (MALT lymphoma) in Mauch et al eds. Non-Hodgkin's Lymphomas. Philadelphia: Lippincott, 2004:352. (http://lww.com)

[a]Single primary or multiple, noncontiguous.

[b]Involvement of multiple extranodal sites in MALT lymphoma appears to be biologically distinct from multiple extranodal involvement in other lymphomas, and these patients may be managed by treating each site separately with excision or RT. In contrast, cases with disseminated nodal involvement appear to behave more like nodal marginal zone lymphoma or like disseminated follicular lymphoma.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines Version 4.2014
Extranodal Marginal Zone B-Cell Lymphoma[a]
Nongastric MALT Lymphoma[b]

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Discussion

DIAGNOSIS

ESSENTIAL:

- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- Adequate immunophenotyping to establish diagnosis[c,d]
  - ➤ IHC panel: CD20, CD3, CD5, CD10, BCL2, kappa lambda, CD21 or CD23, cyclin D1
  - or
  - ➤ Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Molecular analysis to detect: antigen receptor gene rearrangements; MYD88 mutation status to differentiate WM versus MZL if plasmacytic differentiation present; PCR for t(11;18)
- Cytogenetics or FISH: t(11;18), t(11;14), t(3;14)
- FISH or PCR: t(14;18)

WORKUP

ESSENTIAL:

- Physical exam with performance status
- CBC, differential, platelets
- Comprehensive metabolic panel
- LDH
- Hepatitis B testing[e] if rituximab contemplated
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

USEFUL IN SELECTED CASES:

- MUGA scan/echocardiogram if anthracycline or anthracenedione-based regimen is indicated
- Bone marrow biopsy ± aspirate
- Endoscopy with multiple biopsies of anatomical sites[f]
- PET-CT scan
- MRI
- Hepatitis C testing
- Discussion of fertility issues and sperm banking
- SPEP

See Initial Therapy
(NGMLT-2)

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[a]Typical sites of extranodal marginal zone lymphoma other than the stomach include the following: bowel (small and large), breast, head and neck, lung, ocular adnexa, ovary, parotid, prostate, and salivary gland. Infectious agents have been reported to be associated with many nongastric sites, but testing for these agents is not required for management.

[b]This guideline pertains to noncutaneous; for primary cutaneous marginal zone lymphoma, see CUTB.

[c]Typical immunophenotype: CD10-, CD5-, CD20+, CD23-/+, CD43-/+, cyclin D1-, BCL2 follicles.

[d]See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-cell and NK/T-cell Neoplasms (NHODG-A).

[e]Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

[f]In cases where primary site is thought to be in head/neck or lungs, upper GI endoscopy should be considered.

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Extranodal Marginal Zone B-Cell Lymphoma
Nongastric MALT Lymphoma

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Discussion

STAGE **INITIAL THERAPY[i]** **FOLLOW-UP**

Stage I-II →
ISRT[j,k] (preferred)
or
Surgery may be considered for certain sites[l] (lung, breast [lumpectomy], thyroid, colon/small bowel)
or
Rituximab in selected cases
or
Observation in selected cases[m]

→ Positive margins → Consider locoregional RT

→ Negative margins → Observe →

→ Clinical follow-up every 3-6 mo for 5 y and then yearly or as clinically indicated[n]

→ Local recurrence → RT or Manage per follicular lymphoma for advanced stage (FOLL-4)

→ Systemic recurrence → Manage per follicular lymphoma for advanced stage (FOLL-4)

Extranodal (multiple sites)[g] →
RT
or
Observation in selected cases[m]

Stage III, IV: extranodal disease and multiple nodal sites →
Manage per follicular lymphoma for advanced stage (FOLL-4)

Stage I-IV, MALT lymphomas coexistent with large cell lymphoma[h] →
Treat per NCCN Guidelines for Diffuse Large B-Cell Lymphoma (BCEL-1)

[g] Treatment of each site may be indicated (eg, bilateral conjunctiva) both at diagnosis and at relapse.

[h] DLBCL coexistent with MALT cell lymphoma is managed as DLBCL. See NCCN Guidelines for Diffuse Large B-Cell Lymphoma (BCEL-1).

[i] Based on anecdotal responses to antibiotics in ocular and cutaneous marginal zone lymphomas, some physicians will give an empiric course of doxycycline prior to initiating other therapy.

[j] Dose is site dependent with lower dose reserved for eye involvement.

[k] See Principles of Radiation Therapy (NHODG-D).

[l] Surgical excision for adequate diagnosis may be appropriate treatment for disease.

[m] Observation may be considered for patients whose diagnostic biopsy was excisional, or involved-field RT or systemic treatment could result in significant comorbidity.

[n] Follow-up includes diagnostic tests and imaging as clinically indicated.

Note: All recommendations are category 2A unless otherwise indicated.
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Nodal Marginal Zone Lymphoma

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Discussion

DIAGNOSIS[a]

ESSENTIAL:
- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis. Histologic grading cannot be performed on an FNA.
- Adequate immunophenotyping to establish diagnosis[b,c]
  ➤ IHC panel: CD20, CD3, CD5, CD10, BCL2, kappa/lambda, CD21 or CD23, cyclin D1 or
  ➤ Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10
- Pediatric nodal marginal zone lymphoma should be considered with localized disease in a young patient.

USEFUL UNDER CERTAIN CIRCUMSTANCES FOR CLARIFICATION OF DIAGNOSIS:
- Molecular analysis to detect: antigen receptor gene rearrangements; MYD88 mutation status to differentiate WM versus MZL if plasmacytic differentiation present; PCR for t(11;18)
- Cytogenetics or FISH: t(11;18), t(1;14), del(13q), del(7q)
- FISH or PCR: t(14;18)

WORKUP

ESSENTIAL:
- Physical exam with performance status
- CBC, differential, platelets
- Comprehensive metabolic panel
- LDH
- Hepatitis B testing[d] if rituximab contemplated
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Bone marrow biopsy + aspirate to document clinical stage I-II disease[e]
- Evaluation to rule out extranodal primary sites
  ➤ Neck nodes: ocular, parotid, thyroid, and salivary gland
  ➤ Axillary nodes: lung, breast, and skin
  ➤ Mediastinal/hilar nodes: lung
  ➤ Abdominal nodes: splenic and GI
  ➤ Inguinal/iliac nodes: GI and skin
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

USEFUL IN SELECTED CASES:
- MUGA scan/echocardiogram if anthracycline or anthracenedione-based regimen is indicated
- Additional imaging as appropriate
- PET-CT scan
- Hepatitis C testing
- Discussion of fertility issues and sperm banking
- SPEP

Manage per NCCN Guidelines for Follicular Lymphoma (FOLL-2)

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[a] Nodal MZL is rare and occurs most commonly as spread from extranodal MALT; must also be distinguished from nodal FL, MCL, lymphoplasmacytic lymphoma, and CLL, all of which are more common.

[b] Typical immunophenotype: CD10-, CD5-, CD20+, CD23-/+, CD43-/+ and cyclin D1-, BCL2 follicles.

[c] See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).

[d] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

[e] Bilateral or unilateral provided core biopsy is >2 cm. If radioimmunotherapy is considered, bilateral cores are recommended and the pathologist should provide the percent of overall cellular elements and the percent of cellular elements involved in the marrow. If observation is initial therapy, bone marrow biopsy may be deferred.

Note: All recommendations are category 2A unless otherwise indicated.
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Splenic Marginal Zone Lymphoma

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DIAGNOSIS

ESSENTIAL:

- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.[a]
- An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis.
- Adequate immunophenotyping to establish diagnosis[b,c]
  ‣ IHC panel: CD20, CD3, CD5, CD10, BCL2, kappa/lambda, CD21 or CD23, cyclin D1, IgD, CD43, annexin A1; or
  ‣ Cell surface marker analysis by flow cytometry (peripheral blood, bone marrow, or tissue): kappa/lambda, CD19, CD20, CD5, CD23, CD10, CD43, CD103

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Molecular analysis to detect: antigen receptor gene rearrangements; MYD88 mutation status to differentiate WM versus MZL if plasmacytic differentiation present; BRAF mutation status to differentiate MZL from HCL by IHC or sequencing; PCR for t(11;18)
- Cytogenetics or FISH: CLL panel; t(11;18), t(11;14), del(7q)
- FISH or PCR: t(14;18)

[a]SMZL is most definitively diagnosed at splenectomy, since the immunophenotype is nonspecific and morphologic features on the bone marrow may not be diagnostic. However, the diagnosis of SMZL may be made on the basis of bone marrow ± peripheral blood involvement by small lymphoid cells with immunoglobulin (Ig) light chain restriction that lack characteristic features of other small B-cell neoplasms (CD5, CD10, cyclin D1). Plasmacytoid differentiation with cytoplasmic Ig detectable on paraffin sections may occur. In such cases, the differential diagnosis may include lymphoplasmacytic lymphoma. With a characteristic intrasinusoidal lymphocytic infiltration of the bone marrow, the diagnosis can strongly be suggested on bone marrow biopsy alone, if the immunophenotype is consistent.

WORKUP

ESSENTIAL:

- Physical exam with performance status
- CBC, differential, platelets
- Comprehensive metabolic panel
- LDH
- Hepatitis B testing[d] if rituximab contemplated
- Hepatitis C testing
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Bone marrow biopsy ± aspirate
- SPEP and/or quantitative immunoglobulin levels
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

USEFUL IN SELECTED CASES:

- Additional imaging as appropriate
- PET-CT scan
- Discussion of fertility issues and sperm banking
- Immunofixation of blood (for elevated immunoglobulins or positive SPEP)
- Cryoglobulins
- Direct Coombs testing

[b]Typical immunophenotype: CD10-, CD5-, CD20+, CD23-/+, CD43-/+ and cyclin D1-, BCL2 follicles, annexin A1, CD103- (distinction from hairy cell leukemia) with expression of both IgM and IgD.

[c]See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).

[d]Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.
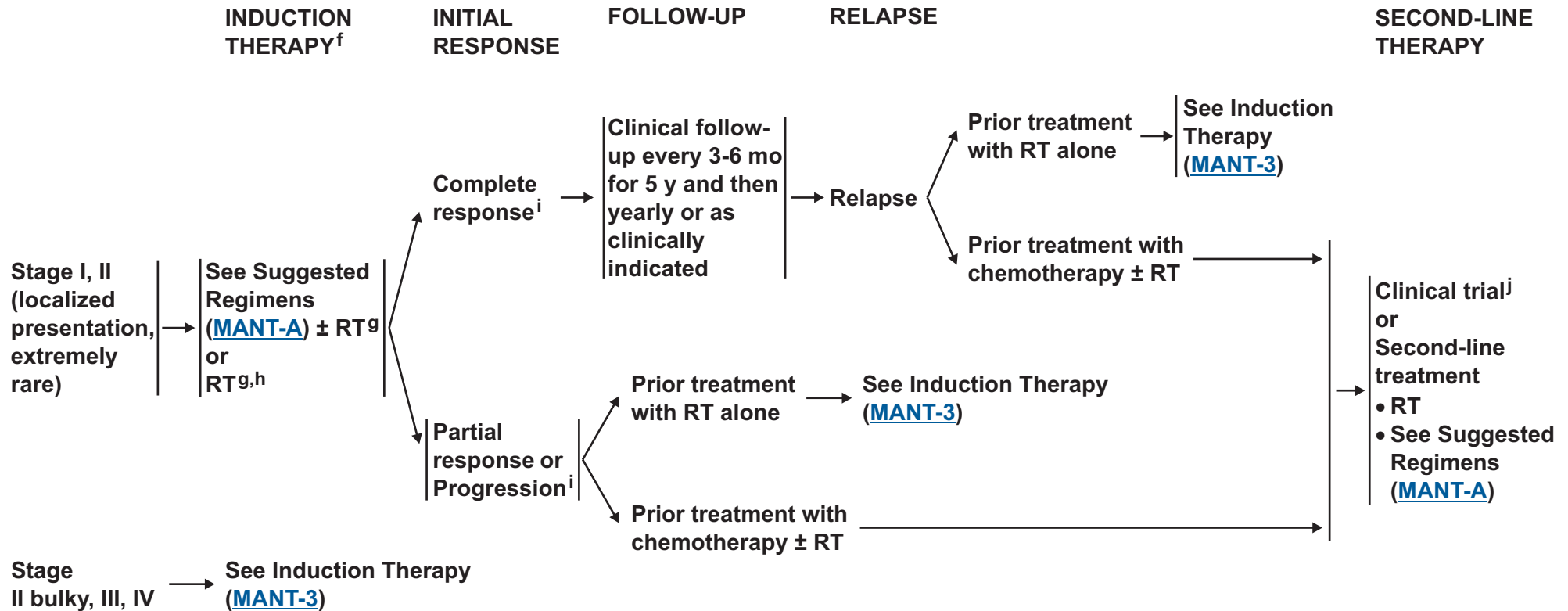
See Management (SPLN-2)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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Splenic Marginal Zone Lymphoma

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CLINICAL PRESENTATION

MANAGEMENT

| Consider prophylaxis for tumor lysis syndrome (See NHODG-B) |
| See monoclonal antibody and viral reactivation (NHODG-B) |

FOLLOW-UP

Asymptomatic, without progressive cytopenia, no splenomegaly → **Observe**

Splenomegaly

→ **Hepatitis C positive** → **Hepatology consult**
- No contraindications for treatment of hepatitis → **Appropriate treatment** → **CR/PR** →
  - **No response** →
- Contraindications for treatment of hepatitis →

→ **Hepatitis C negative** → **Assess**
- • Cytopenias • Symptoms → **Splenectomy[e] or Rituximab[f]** →
- No symptoms → **Observe**

Clinical follow-up every 3-6 mo for 5 y and then yearly or as clinically indicated[g] → **If progression of disease, manage per NCCN Guidelines for Follicular Lymphoma for advanced stage (FOLL-4)**

[e] Pneumococcal and meningococcal vaccination should be performed at least 2 weeks before splenectomy.

[f] Tsimberidou AM, Catovsky D, Schlette E, et al. Outcomes in patients with splenic marginal zone lymphoma and marginal zone lymphoma treated with rituximab with or without chemotherapy or chemotherapy alone. Cancer 2006;107:125-135.

[g] Follow-up includes diagnostic tests and imaging as clinically indicated.

Note: All recommendations are category 2A unless otherwise indicated.
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Mantle Cell Lymphoma

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DIAGNOSIS

ESSENTIAL:

- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis.
- Adequate immunophenotyping to establish diagnosis[a,b]
  - IHC panel: CD20, CD3, CD5, cyclin D1, CD10, CD21, CD23, BCL2, BCL6, Ki-67[c]
    or
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- Molecular analysis to detect: antigen receptor gene rearrangements; *CCND1* rearrangements
- Cytogenetics or FISH: t(11;14), t(14;18), CLL panel

WORKUP

ESSENTIAL:

- Physical exam: Attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC, differential, platelets
- Comprehensive metabolic panel
- LDH
- Bone marrow biopsy ± aspirate
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Hepatitis B testing[d] if rituximab contemplated
- MUGA scan/echocardiogram if anthracycline or anthracenedione-based regimen is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- Endoscopy/colonoscopy[e]
- Neck CT
- Uric acid
- Discussion of fertility issues and sperm banking
- Lumbar puncture (for blastic variant or CNS symptoms)
- Beta-2-microglobulin
- PET-CT scan

See Induction Therapy (MANT-2)

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[a] Typical immunophenotype: CD5+, CD20+, CD43+, CD23-/+, cyclin D1+, CD10-/+. Note: Some cases of MCL may be CD5- or CD23+. If the diagnosis is suspected, cyclin D1 staining or FISH for t(11;14) should be done. There are rare cases of *CCND1*- MCL (<5%) with an otherwise typical immunophenotype.

[b] See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).

[c] Ki-67 proliferation fraction of <30% is associated with a more favorable prognosis. However, it is not used to guide treatment.

[d] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

[e] Essential for confirmation of stage I-II disease. See Discussion for details.

Note: All recommendations are category 2A unless otherwise indicated.
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Mantle Cell Lymphoma

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INDUCTION THERAPY[f]	INITIAL RESPONSE	FOLLOW-UP	RELAPSE		SECOND-LINE THERAPY

Stage I, II (localized presentation, extremely rare) → **See Suggested Regimens (MANT-A) ± RT[g] or RT[g,h]**

Complete response[i] → **Clinical follow-up every 3-6 mo for 5 y and then yearly or as clinically indicated** → **Relapse**

Relapse → **Prior treatment with RT alone** → **See Induction Therapy (MANT-3)**

Relapse → **Prior treatment with chemotherapy ± RT** →

Partial response or Progression[i] →

Prior treatment with RT alone → **See Induction Therapy (MANT-3)**

Prior treatment with chemotherapy ± RT →

Clinical trial[j] or Second-line treatment
- RT
- See Suggested Regimens (MANT-A)

Stage II bulky, III, IV → **See Induction Therapy (MANT-3)**

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

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[f]Early referral for high-dose therapy with stem cell rescue is advisable for planning purposes.
[g]See Principles of Radiation Therapy (NHODG-D).
[h]Leitch HA, Gascoyne RD, Chhanabhai M, et al. Limited-stage mantle-cell lymphoma. Ann Oncol 2003;14:1555-1561.

[i]See Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[j]Option for clinical trials of adjuvant therapy or for relapsed disease involving high-dose therapy with autologous or allogeneic stem cell rescue, immunotherapy with nonmyeloablative stem cell rescue, or evaluation of treatment with new agents are appropriate.

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INDUCTION THERAPY[f] | **INITIAL RESPONSE** | **CONSOLIDATION** | **FOLLOW-UP** | **RELAPSE** | **SECOND-LINE THERAPY**

Stage II bulky, III, IV →

Clinical trial or See Suggested Regimens (MANT-A) or Observation in highly selected cases[k]

Complete response[i]

Candidate for HDT/ASCR →
- Clinical trial
- High-dose therapy with autologous stem cell rescue

Not candidate for HDT/ASCR

Treated with RCHOP → Rituximab maintenance (category 1) (See MANT-A)

Not treated with RCHOP

Clinical follow-up every 3-6 mo for 5 y and then yearly or as clinically indicated → Relapse

Partial response[i] → Consider second-line therapy (See MANT-A)

CR/Improved PR

No further response

Progression[i]

Clinical trial[j] or Second-line treatment
- RT
- See Suggested Regimens (MANT-A)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

[f]Early referral for high-dose therapy with stem cell rescue is advisable for planning purposes.

[i]See Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).

[j]Option for clinical trials of adjuvant therapy or for relapsed disease involving high-dose therapy with autologous stem cell rescue or allogeneic stem cell transplant, immunotherapy with nonmyeloablative stem cell rescue, or evaluation of treatment with new agents are appropriate.

[k]Martin P, Chadburn A, Christos P, et al. Outcome of deferred initial therapy in mantle-cell lymphoma. J Clin Oncol 2009;27:1209-1213.

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SUGGESTED TREATMENT REGIMENS[a]
(in alphabetical order)

Induction Therapy

- **Aggressive therapy**
  - ➤ **CALGB regimen**[b] **(Treatment 1, 2, 2.5: rituximab + methotrexate with augmented CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone]; Treatment 3: etoposide, cytarabine, rituximab; Treatment 4: carmustine, etoposide, cyclophosphamide/autologous stem cell rescue; Treatment 5: rituximab maintenance) (Treatment 2.5 is given if the pre-Treatment 3 bone marrow biopsy contains >15% MCL.)**
  - ➤ **HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab**
  - ➤ **NORDIC regimen**[b] **(dose-intensified induction immunochemotherapy with rituximab + cyclophosphamide, vincristine, doxorubicin, prednisone [maxi-CHOP]) alternating with rituximab + high-dose cytarabine)**
  - ➤ **Alternating RCHOP/RDHAP**[b] **(rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)/(rituximab, dexamethasone, cisplatin, cytarabine)**
  - ➤ **Sequential RCHOP/RICE**[b] **(rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)/(rituximab, ifosfamide, carboplatin, etoposide)**
- **Less aggressive therapy**
  - ➤ **Bendamustine + rituximab**
  - ➤ **CHOP + rituximab**[c] **followed by consolidation with rituximab maintenance (375 mg/m^2 every 8 wks until progression) (category 1 for maintenance)**
  - ➤ **Cladribine + rituximab**
  - ➤ **Modified rituximab-HyperCVAD with rituximab maintenance in patients older than 65 y**

First-line Consolidation[d]

- **Clinical trial**
- **High-dose therapy with autologous stem cell rescue**[e]

Second-line Therapy

- **Bendamustine ± rituximab**
- **Bortezomib ± rituximab**
- **Cladribine + rituximab**
- **FC (fludarabine, cyclophosphamide) ± rituximab**
- **FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab)**
- **FMR (fludarabine, mitoxantrone, rituximab)**
- **Ibrutinib**[f]
- **Lenalidomide ± rituximab**
- **PCR (pentostatin, cyclophosphamide, rituximab)**
- **PEPC (prednisone, etoposide, procarbazine, cyclophosphamide) ± rituximab**
- **See Second-line Therapy for DLBCL (BCEL-C 1 of 3)** without regard to transplantability

Second-line Consolidation

- **Allogeneic stem cell transplant (nonmyeloablative or myeloablative)**

> **Consider prophylaxis for tumor lysis syndrome (See NHODG-B)**
>
> **See monoclonal antibody and viral reactivation (NHODG-B)**

[a]See references for regimens MANT-A 2 of 3 and MANT-A 3 of 3.

[b]These regimens include first-line consolidation with high-dose therapy and autologous stem cell rescue (HDT/ASCR).

[c]There is a randomized trial that demonstrated that RCHOP was not superior to CHOP.

[d]Typically patients will receive an aggressive induction regimen prior to consolidation; however, less aggressive regimens followed by consolidation with high-dose therapy may also result in a good long-term outcome.

[e]Randomized data with anthracycline-containing regimens suggest an improvement in progression-free survival with the addition of first-line high-dose therapy with autologous stem cell consolidation.

[f]See Special Considerations for Use of B-Cell Receptor Inhibitors (Ibrutinib and Idelalisib) (NHODG-E).

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References

Induction Therapy
Aggressive therapy
HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with methotrexate and cytarabine) + rituximab
Romaguera JE, Fayad L, Rodriguez MA, et al. High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. J Clin Oncol 2005;23:7013-7023.

Merli F, Luminari S, Ilariucci F, et al. Rituximab plus HyperCVAD alternating with high dose cytarabine and methotrexate for the initial treatment of patients with mantle cell lymphoma, a multicentre trial from Gruppo Italiano Studio Linfomi. Br J Haematol 2012;156:346-353.

Nordic trial regimen (Dose-intensified induction immunochemotherapy with rituximab + cyclophosphamide, vincristine, doxorubicin, prednisone [maxi-CHOP]) alternating with rituximab + high-dose cytarabine)
Geisler CH, Kolstad A, Laurell A, et al. Long-term progression-free survival of mantle cell lymphoma following intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: A non-randomized phase-II multicenter study by the Nordic Lymphoma Group. Blood 2008;112:2687-2693.

CALGB regimen
Damon LE, Johnson JL, Niedzwiecki D, et al. Immunochemotherapy and autologous stem-cell transplantation for untreated patients with mantle-cell lymphoma: CALGB 59909. J Clin Oncol 2009;27:6101-6108.

RCHOP/RICE
Schaffel R, Hedvat CV, Teruya-Feldstein J, et al. Prognostic impact of proliferative index determined by quantitative image analysis and the International Prognostic Index in patients with mantle cell lymphoma. Ann Oncol 2010;21:133-139.

RCHOP/RDHAP
Pott C, Hoster E, Beldjord K, et al. R-CHOP/R-DHAP compared to R-CHOP induction followed by high dose therapy with autologous stem cell transplantation induces higher rates of molecular remission in MCL: Results of the MCL Younger Intergroup Trial of the European MCL Network [abstract]. Blood 2010;116:Abstract 965.

Delarue R, Haioun C, Ribrag V, et al. CHOP and DHAP plus rituximab followed by autologous stem cell transplantation (ASCT) in mantle cell lymphoma (MCL): a phase II study from the GELA. Blood 2013;121:48-53.

Less aggressive therapy
Bendamustine + rituximab
Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet 2013;381:1203-1210.

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab
Lenz G, Dreyling M, Hoster E, et al. Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). J Clin Oncol 2005;23:1984-1992.

Kluin-Nelemans HC, Hoster E, Hermine O, et al. Treatment of older patients with mantle-cell lymphoma. N Eng J Med 2012;367:520-531.

Cladribine + rituximab
Inwards DJ, Fishkin PA, Hillman DW, et al. Long-term results of the treatment of patients with mantle cell lymphoma with cladribine (2-CDA) alone (95-80-53) or 2-CDA and rituximab (N0189) in the North Central Cancer Treatment Group. Cancer 2008;113:108-116.

Spurgeon SE, Pindyck T, Okada C, et al. Cladribine plus rituximab is an effective therapy for newly diagnosed mantle cell lymphoma. Leuk Lymphoma 2011;52:1488-1494.

Modified HyperCVAD with rituximab maintenance
Kahl BS, Long WL, Eickhoff JC, et al. Maintenance rituximab following induction chemoimmunotherapy may prolong progression-free survival in mantle cell lymphoma: A pilot study from the Wisconsin Oncology Network. Ann Oncol 2006;17:1418-1423.

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First-line Consolidation
High-dose therapy with autologous stem cell rescue
Dreyling M, Lenz G, Hoster E, et al. Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle cell lymphoma: results of a prospective randomized trial of the European MCL Network. Blood 2005;105:2677-2684.

Thieblemont C, Antal D, Lacotte-Thierry L, et al. Chemotherapy with rituximab followed by high-dose therapy and autologous stem cell transplantation in patients with mantle cell lymphoma. Cancer 2005;104:1434-1441.

Ritchie D, Seymour J, Grigg A, et al. The hyper-CVAD–rituximab chemotherapy programme followed by high-dose busulfan, melphalan and autologous stem cell transplantation produces excellent event-free survival in patients with previously untreated mantle cell lymphoma. Ann Hematol 2007;86:101-105.

van 't Veer MB, de Jong D, MacKenzie M, et al. High-dose Ara-C and beam with autograft rescue in R-CHOP responsive mantle cell lymphoma patients. Br J Haematol 2009;144:524-530.

Rituximab maintenance
Kluin-Nelemans HC, Hoster E, Hermine O, et al. Treatment of older patients with mantle-cell lymphoma. N Engl J Med 2012;367:520-531.

Second-line Therapy
Bendamustine
Robinson KS, Williams ME, van der Jagt RH, et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell Non-Hodgkin's Lymphoma. J Clin Oncol 2008; 26:4473-4479.

Rummel MJ, Al-Batran SE, Kim S-Z, et al. Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-hodgkin's lymphoma. J Clin Oncol 2005;23:3383-3389.

Bortezomib
Goy A, Bernstein SH, Kahl BS, et al. Bortezomib in patients with relapsed or refractory mantle cell lymphoma: updated time-to-event analyses of the multicenter phase 2 PINNACLE study. Ann Oncol 2009;20:520-525.

Baiocchi RA, Alinari L, Lustberg ME, et al. Phase 2 trial of rituximab and bortezomib in patients with relapsed or refractory mantle cell and follicular lymphoma. Cancer 2011;117:2442-2451.

Cladribine
Rummel MJ, Chow KU, Jager E, et al. Treatment of mantle-cell lymphomas with intermittent two-hour infusion of cladribine as first-line therapy or in first relapse. Ann Oncol 1999;10:115-117.

Inwards DJ, Fishkin PA, Hillman DW, et al. Long-term results of the treatment of patients with mantle cell lymphoma with cladribine (2-CDA) alone (95-80-53) or 2-CDA and rituximab (N0189) in the North Central Cancer Treatment Group. Cancer 2008;113:108-116.

FC (fludarabine and cyclophosphamide) ± rituximab
Cohen BJ, Moskowitz C, Straus D et al. Cyclophosphamide/fludarabine (CF) is active in the treatment of mantle cell lymphoma. Leuk Lymphoma 2001;42:1015-1022.

FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab)
Forstpointner R, Dreyling M, Repp R, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared to FCM alone in patients with relapsed and refractory follicular and mantle cell lymphoma - results of a prospective randomized study of the German low grade lymphoma study group (GLSG). Blood 2004;104:3064-3071.

FMR (fludarabine, mitoxantrone, rituximab)
Levine AM, Tulpule A, Smith L, Espina BM, Mohrbacher AF, Feinstein DI. Results of a pilot trial of fludarabine, mitoxantrone and rituxan in mantle cell lymphoma [abstract]. Blood 2005;106:Abstract 945.

Ibrutinib
Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Eng J Med 2013;369:507-516.

Lenalidomide
Habermann TM, Lossos IS, Justice G, et al. Lenalidomide oral monotherapy produces a high response rate in patients with relapsed or refractory mantle cell lymphoma. Br J Haematol 2009;145:344-349.

Witzig TE, Vose JM, Zinzani PL, et al. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. Ann Oncol 2011;22:1622-1627.

Goy A, Sinha R, Williams ME, et al. Phase II multicenter study of single-agent lenalidomide in subjects with mantle cell lymphoma who relapsed or progressed after or were refractory to bortezomib: the MCL-001 "EMERGE" Study [abstract]. Blood 2012;120:Abstract 905.

Lenalidomide + rituximab
Wang M, Fayad L, Wagner-Bartak N, et al. Lenalidomide in combination with rituximab for patients with relapsed or refractory mantle-cell lymphoma: a phase 1/2 clinical trial. Lancet Oncol 2012;13:716-723.

PEP-C (prednisone, etoposide, procarbazine, cyclophosphamide) ± rituximab
Coleman M, Martin P, Ruan J, et al. Prednisone, etoposide, procarbazine, and cyclophosphamide (PEP-C) oral combination chemotherapy regimen for recurring/refractory lymphoma: low-dose metronomic, multidrug therapy. Cancer 2008;112:2228-2232.

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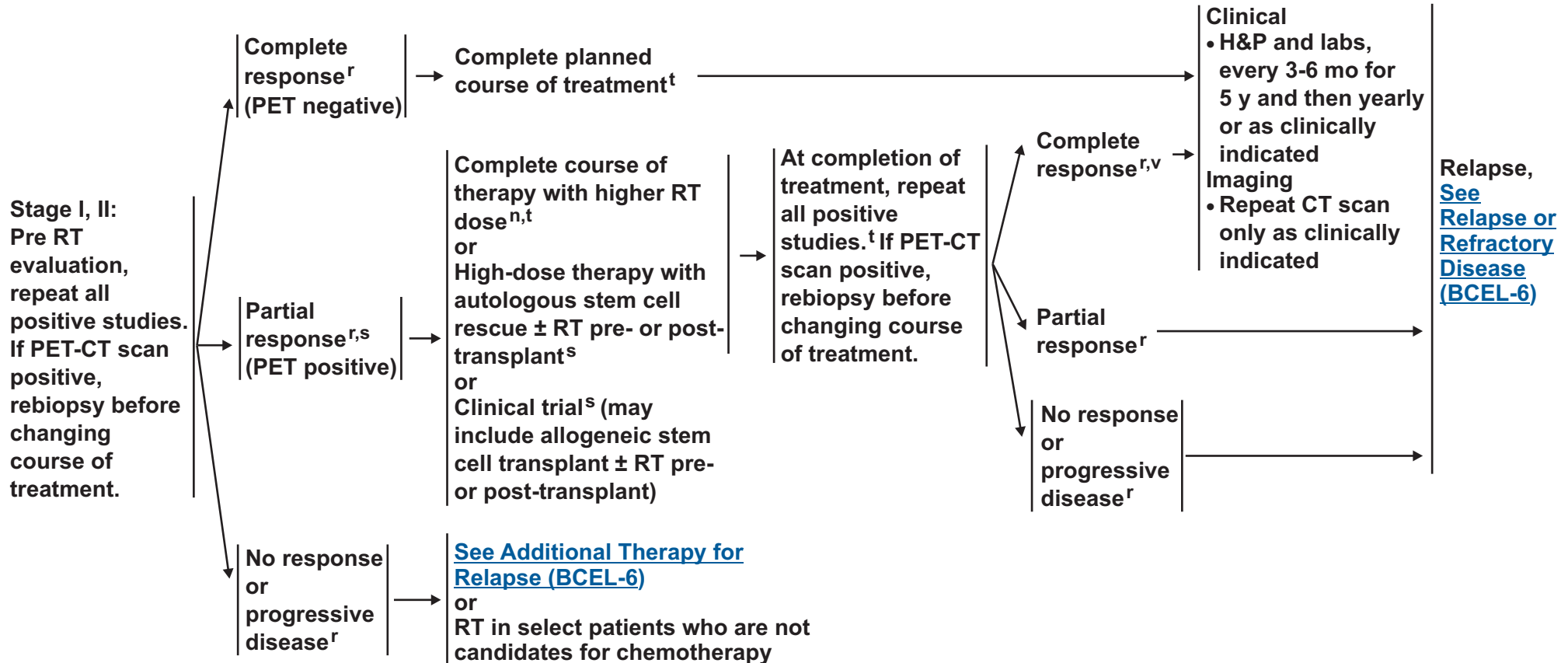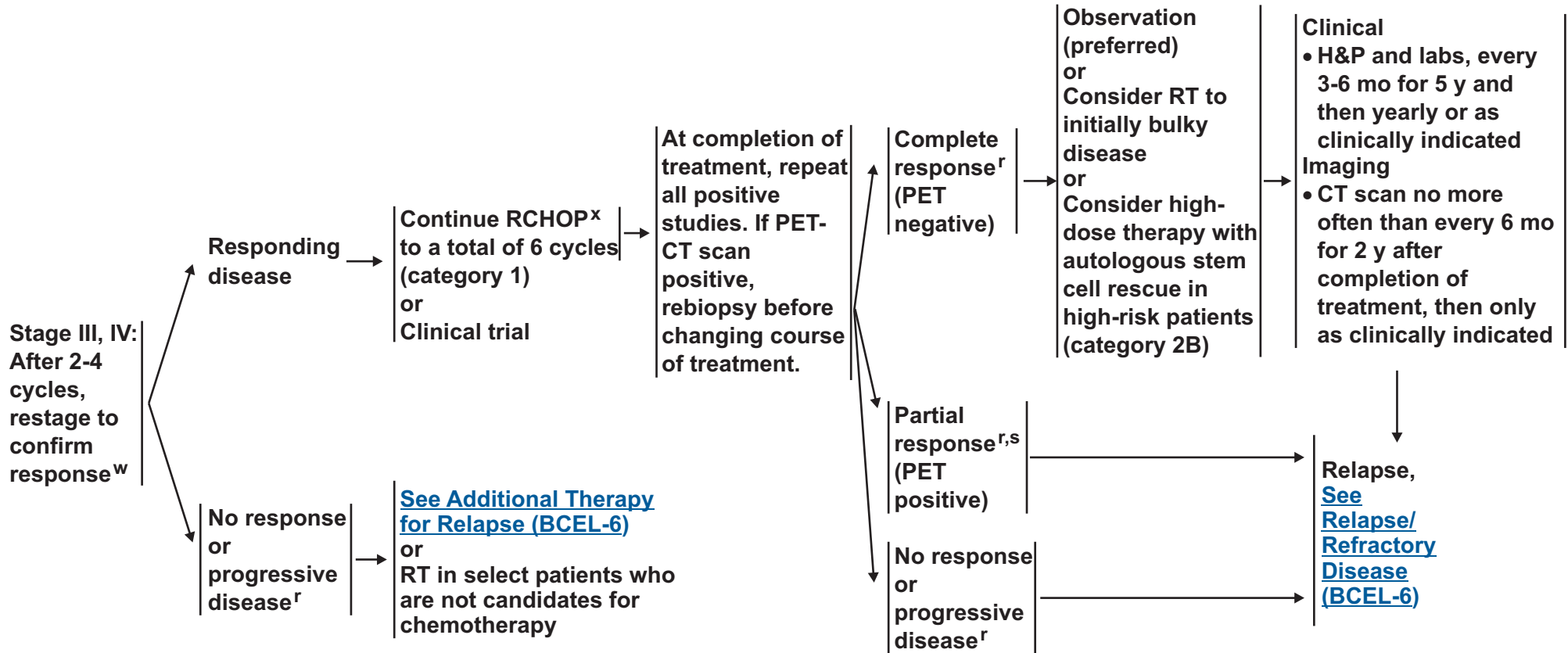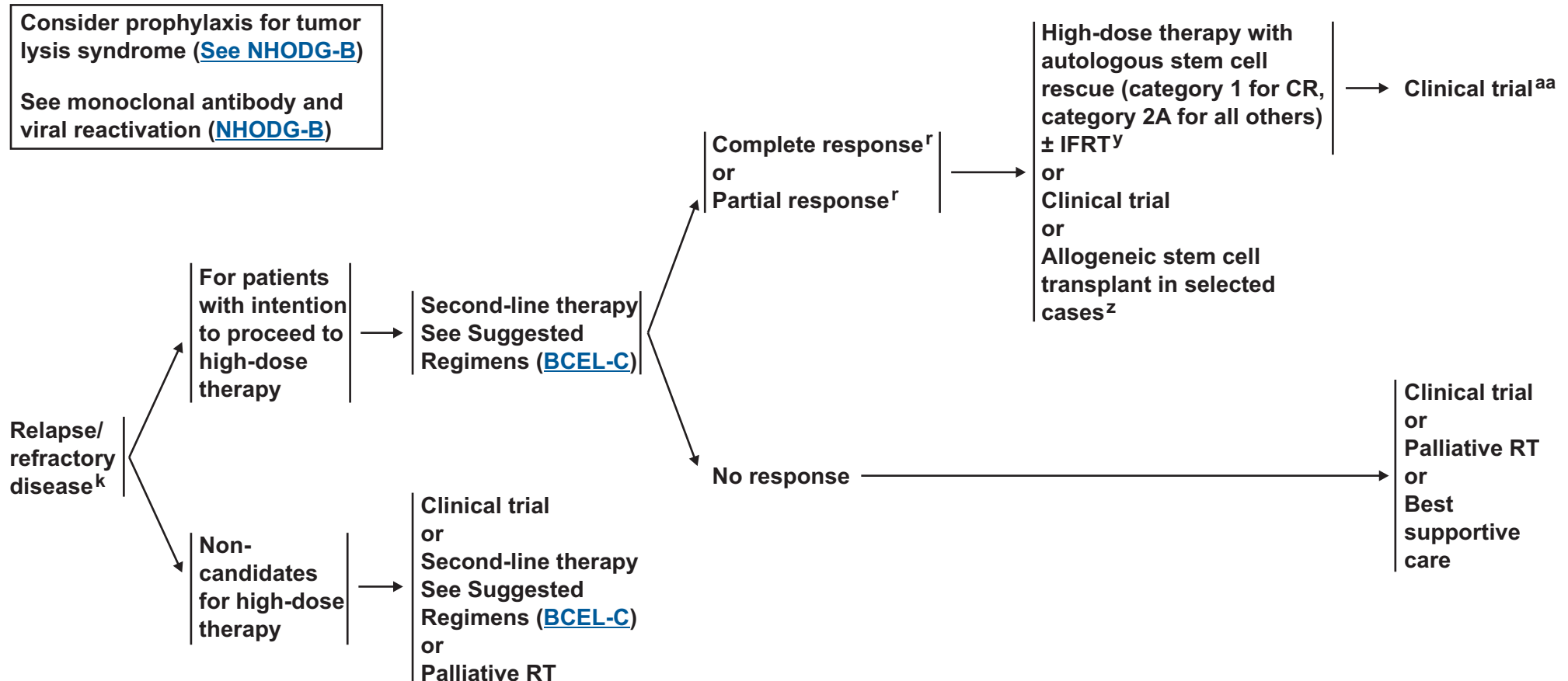
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DIAGNOSIS[a,b]

ESSENTIAL:

- **Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.**
- **An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis.**
- **Adequate immunophenotyping to establish diagnosis and GCB versus non-GCB origin[c,d]**
  - **IHC panel: CD20, CD3, CD5, CD10, CD45, BCL2, BCL6, Ki-67, IRF4/MUM1, MYC**
    or
  - **Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD3, CD5, CD19, CD10, CD20**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **Additional immunohistochemical studies to establish lymphoma subtype**
  - **IHC panel: Cyclin D1, kappa/lambda, CD30, CD138, EBER-ISH, ALK, HHV8**
- **Cytogenetics or FISH: t(14;18),[e] t(3;v), t(8;14), t(8;v)**

SUBTYPES

- **Subtypes included:**
  - **DLBCL, NOS[f]**
  - **DLBCL coexistent with follicular lymphoma of any grade**
  - **DLBCL coexistent with gastric MALT lymphoma**
  - **DLBCL coexistent with nongastric MALT lymphoma**
  - **Follicular lymphoma grade 3**
  - **Intravascular large B-cell lymphoma**
  - **DLBCL associated with chronic inflammation**
  - **ALK-positive DLBCL**
  - **EBV-positive DLBCL of the elderly**
  - **T-cell-/histiocyte-rich large B-cell lymphoma**

→ **See Workup (BCEL-2)**

- **Subtypes *not* included:**
  - **Primary cutaneous B-cell lymphomas (See CUTB-1)**
  - **Primary DLBCL of the CNS (See NCCN Guidelines for CNS)**

Primary Mediastinal Large B-Cell Lymphoma (PMBL), see BCEL-B 1 of 2.
Grey Zone Lymphoma, see BCEL-B 2 of 2.

[c] Typical immunophenotype: CD20+, CD45+, CD3-; other markers used for subclassification.
[d] See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).
[e] There are no established guidelines to select DLBCL patients to investigate for double-hit lymphomas. Standard of care is not established for DLBCL with t(14;18) with concurrent MYC rearrangements.
[f] Germinal center (or follicle center) cell phenotype is not equivalent to follicular lymphoma and can occur in DLBCL and Burkitt lymphoma. Morphology is required to establish diagnosis.

[a] Burkitt lymphoma intermediate histology or DLBCL CD10 + tumors with very high proliferation >90% with or without Burkitt lymphoma-like features might be considered for more aggressive treatment as per BURK-A. These cases would be appropriate to evaluate for *BCL2*, *BCL6,* and *MYC* rearrangements.
[b] See International Prognostic Index (BCEL-A).

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WORKUP

ESSENTIAL:
- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC, differential, platelets
- LDH
- Comprehensive metabolic panel
- Uric acid
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- PET-CT scan
- Adequate bone marrow biopsy (>1.6 cm) ± aspirate
- Calculation of International Prognostic Index (IPI)[b]
- Hepatitis B testing[g]
- MUGA scan/echocardiogram if anthracycline or anthracenedione-based regimen is indicated
- Pregnancy testing in women of child-bearing age
- Beta-2-microglobulin (category 2B)

USEFUL IN SELECTED CASES:
- Neck CT, head CT, or MRI
- Discussion of fertility issues and sperm banking
- HIV
- Lumbar puncture, if paranasal sinus, testicular, epidural, bone marrow with large cell lymphoma, HIV lymphoma, or ≥2 extranodal sites and elevated LDH

See Induction
Therapy (BCEL-3)

[b] See International Prognostic Index (BCEL-A).

[g] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

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STAGE	INDUCTION THERAPY[l]

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

Stage I, II[h,i]

→ **Nonbulky (<10 cm)** → RCHOP[m] x 3 cycles + RT[n] or RCHOP[m] x 6 cycles ± RT[n] → **See Pre RT Evaluation (BCEL-4)**

→ **Bulky (≥10 cm)** → RCHOP[m] x 6 cycles ± RT[n] (category 1) → **See Pre RT Evaluation (BCEL-4)**

Stage III, IV[h,j,k] → Clinical trial[o] or RCHOP[p] (category 1)[q] → **After 2-4 cycles** → **See Interim Restaging (BCEL-5)**

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[h]In testicular lymphoma, after completion of chemotherapy, scrotal RT should be given (25-30 Gy).

[i]In patients who are not candidates for chemotherapy, involved-site radiation therapy (ISRT) is recommended.

[j]In selected cases (paranasal sinus, testicular, epidural, bone marrow with large cell lymphoma, HIV lymphoma, or ≥2 extranodal sites and elevated LDH), there may be an increased risk of CNS events. The optimal management of these events is uncertain, but CNS prophylaxis can be considered with 4-8 doses of intrathecal methotrexate and/or cytarabine, or systemic methotrexate $(3-3.5 \text{ g/m}^2)$ during the course of treatment. Recent data regarding stage IE DLBCL of the breast have been suggested as a potential risk for CNS disease.

[k]For systemic disease with concurrent CNS disease, see BCEL-C.

[l]Recommendations are for HIV-negative lymphoma only. For HIV-positive DLBCL, see AIDS-2.

[m]For patients who cannot tolerate anthracyclines, see BCEL-C for regimens for patients with poor left ventricular function.

[n]See Principles of Radiation Therapy (NHODG-D).

[o]May include high-dose therapy.

[p]Based on current clinical trials, CHOP is preferable due to reduced toxicities, but other comparable anthracycline-based regimens are acceptable (see BCEL-C).

[q]In selected cases, RT to initially bulky sites of disease may be beneficial (category 2B).

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PRE RT EVALUATION
(End of induction chemoimmunotherapy)

FOLLOW-UP THERAPY

END OF TREATMENT RESTAGING[u]

INITIAL RESPONSE (after completion of induction chemotherapy)

FOLLOW-UP

Stage I, II: Pre RT evaluation, repeat all positive studies. If PET-CT scan positive, rebiopsy before changing course of treatment.

Complete response[r] (PET negative) → Complete planned course of treatment[t] →

Partial response[r,s] (PET positive) → Complete course of therapy with higher RT dose[n,t] or High-dose therapy with autologous stem cell rescue ± RT pre- or post-transplant[s] or Clinical trial[s] (may include allogeneic stem cell transplant ± RT pre- or post-transplant) → At completion of treatment, repeat all positive studies.[t] If PET-CT scan positive, rebiopsy before changing course of treatment.

No response or progressive disease[r] → **See Additional Therapy for Relapse (BCEL-6)** or RT in select patients who are not candidates for chemotherapy

Complete response[r,v] → **Clinical**
- H&P and labs, every 3-6 mo for 5 y and then yearly or as clinically indicated

Imaging
- Repeat CT scan only as clinically indicated

Partial response[r]

No response or progressive disease[r]

Relapse, See Relapse or Refractory Disease (BCEL-6)

[n] See Principles of Radiation Therapy (NHODG-D).
[r] See Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[s] Repeat biopsy should be strongly considered in PET positive prior to additional therapy.
[t] The optimum timing of repeat PET-CT is unknown; however, waiting a minimum of 8 weeks after RT to repeat PET-CT scan is suggested. False positives may occur due to posttreatment changes.
[u] There is evidence that addition of maintenance rituximab does not improve survival.
[v] Patients in first remission may be candidates for consolidation trials including high-dose therapy with autologous stem cell rescue.

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INTERIM RESTAGING | **FOLLOW-UP THERAPY** | **END-OF-TREATMENT RESTAGING[u]** | **INITIAL RESPONSE (after completion of induction chemotherapy)** | **FOLLOW-UP**

Stage III, IV: After 2-4 cycles, restage to confirm response[w]

→ **Responding disease** → **Continue RCHOP[x] to a total of 6 cycles (category 1) or Clinical trial**

→ **No response or progressive disease[r]** → **See Additional Therapy for Relapse (BCEL-6) or RT in select patients who are not candidates for chemotherapy**

At completion of treatment, repeat all positive studies. If PET-CT scan positive, rebiopsy before changing course of treatment.

→ **Complete response[r] (PET negative)** → **Observation (preferred) or Consider RT to initially bulky disease or Consider high-dose therapy with autologous stem cell rescue in high-risk patients (category 2B)**

→ **Partial response[r,s] (PET positive)** → **Relapse, See Relapse/Refractory Disease (BCEL-6)**

→ **No response or progressive disease[r]** → **Relapse, See Relapse/Refractory Disease (BCEL-6)**

Clinical
- H&P and labs, every 3-6 mo for 5 y and then yearly or as clinically indicated

Imaging
- CT scan no more often than every 6 mo for 2 y after completion of treatment, then only as clinically indicated

[r] See Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[s] Repeat biopsy should be strongly considered in PET positive prior to additional therapy.
[u] There is evidence that the addition of maintenance rituximab does not improve survival..
[w] PET-CT scan at interim restaging can lead to increased false positives and should be carefully considered in select cases. If PET-CT scan performed and positive, rebiopsy before changing course of treatment.
[x] For other regimens, see BCEL-C.

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RELAPSE/ REFRACTORY DISEASE	ADDITIONAL THERAPY	RESPONSE #2	CONSOLIDATION/ ADDITIONAL THERAPY	RELAPSE #2 OR GREATER

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

Relapse/ refractory disease[k]

For patients with intention to proceed to high-dose therapy → **Second-line therapy See Suggested Regimens (BCEL-C)**

Complete response[r] or Partial response[r] → **High-dose therapy with autologous stem cell rescue (category 1 for CR, category 2A for all others) ± IFRT[y] or Clinical trial or Allogeneic stem cell transplant in selected cases[z]** → **Clinical trial[aa]**

No response →

Non-candidates for high-dose therapy → **Clinical trial or Second-line therapy See Suggested Regimens (BCEL-C) or Palliative RT**

Clinical trial or Palliative RT or Best supportive care

[k] For systemic disease with concurrent CNS disease, see BCEL-C.

[r] See Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).

[y] Additional RT can be given before or after high-dose therapy with stem cell rescue to sites of previous positive disease.

[z] Selected cases include mobilization failures and persistent bone marrow involvement.

[aa] Clinical trials or individual regimens: Patients who progress after three successive regimens are unlikely to derive additional benefit from currently utilized combination chemotherapy regimens, except for patients with a long disease-free interval.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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INTERNATIONAL PROGNOSTIC INDEX[a]

ALL PATIENTS:
- Age >60 years
- Serum LDH > normal
- Performance status 2-4
- Stage III or IV
- Extranodal involvement >1 site

INTERNATIONAL INDEX, ALL PATIENTS:
- Low   0 or 1
- Low intermediate   2
- High intermediate   3
- High   4 or 5

AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX[a]

PATIENTS ≤60 YEARS:
- Stage III or IV
- Serum LDH > normal
- Performance status 2-4

INTERNATIONAL INDEX, PATIENTS ≤60 YEARS:
- Low   0
- Low/intermediate   1
- High/intermediate 2
- High   3

[a]The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-hodgkin's lymphoma. N Engl J Med 1993; 329:987-994.

Back to Workup (BCEL-1)

Note: All recommendations are category 2A unless otherwise indicated.
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Primary Mediastinal Large B-Cell Lymphoma

Primary mediastinal large B-cell lymphoma (PMBL) can be defined as a clinical entity presenting with primary site of disease in mediastinum with or without other sites and has histology of DLBCL. PBML overlaps with grey zone lymphomas that have intermediate features between Hodgkin lymphoma and PMBL and have unique diagnostic characteristics.
See Grey Zone Lymphoma (BCEL-B 2 of 2).

- Clinical pathologic correlation is required to establish diagnosis.

- Optimal first-line therapy is more controversial than other subtypes of NHL; however, treatment regimens include:
  ‣ RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) x 6 cycles + RT
  ‣ Dose-adjusted EPOCH-R ([etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin] + rituximab)[a] x 6 cycles; for persistent focal disease, RT can be added.
  ‣ RCHOP x 4 cycles followed by ICE (ifosfamide, carboplatin, etoposide)[b] x 3 cycles ± RT (category 2B)

- Role of RT is controversial. If PET-CT scan was negative at the end of treatment and initial disease was non-bulky, observation may be considered.

- Residual mediastinal masses are common. PET-CT scan is essential post-treatment. Biopsy of PET-CT scan positive mass is recommended if additional systemic treatment is contemplated.

[a]Dunleavy K, Pittaluga S, Maeda LS, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. N Engl J Med 2013;368:1408-1416.
[b]Moskowitz C, Hamlin PA, Jr., Maragulia J, et al. Sequential dose-dense RCHOP followed by ICE consolidation (MSKCC protocol 01-142) without radiotherapy for patients with primary mediastinal large B-cell lymphoma [abstract]. Blood 2010;116:Abstract 420.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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Grey Zone Lymphoma

Synonyms
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma (CHL)
- Large B-cell lymphoma with Hodgkin features
- Hodgkin-like anaplastic large cell lymphoma

Clinical Presentation
- Present with large anterior mediastinal mass with or without supraclavicular lymph nodes
  ‣ More common in males, presenting between 20-40 y

Morphology
- Pleomorphic cells in a diffusely fibrous stroma
- Typically larger and more pleomorphic than in PMBL, sometimes resembling lacunar or Hodgkin-like cells
- Necrosis without neutrophilic infiltrate is frequent

Immunophenotype
- Often transitional features between CHL and PMBL
- CD45 often positive; CD30, CD15, CD20, CD79a frequently positive
- EBV - (<20% of cases +)
- PAX5, BOB.1, OCT-2 are often positive, BCL6 variable
- CD10, ALK are negative
- If morphology closer to PMBL, absence of CD20, CD15+ or the presence of EBV would suggest the diagnosis of grey zone lymphoma
- If morphology closer to CHL, CD20 strong positivity and other B-cell markers and absence of CD15 would suggest grey zone lymphoma.

Prognosis and Treatment
- A worse prognosis than either CHL or PMBL has been suggested.
- While there is no consensus on the treatment, aggressive large B-cell lymphoma [or Hodgkin type] regimens have been proposed.
- If the tumor cells are CD20+, the addition of rituximab to the chemotherapy treatment should be considered.
- Data from the NIH suggest that the use of dose-adjusted R-EPOCH is helpful. If localized disease, then ± RT.

References:

Dunleavy K, Pittaluga S, Tay K, et al. Comparative clinical and biological features of primary mediastinal B-cell lymphoma (PMBL) and mediastinal grey zone lymphoma (MGZL) [abstract]. Blood 2009;114:Abstract 106.

Jaffe ES, Stein H, Swerdlow SH, et al. B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:267-268.

Quintanilla-Martinez L, de Jong D, de Mascarel A, et al. Gray zones around diffuse large B cell lymphoma. Conclusions based on the workshop of the XIV meeting of the European Association for Hematopathology and the Society of Hematopathology in Bordeaux, France. J Hematop 2009;2:211-236.

Note: All recommendations are category 2A unless otherwise indicated.
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SUGGESTED TREATMENT REGIMENS[a]
(in alphabetical order)

First-line Therapy
- RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)
- Dose-dense RCHOP 14 (category 3)
- Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab (category 2B)

First-line Therapy for Patients with Poor Left Ventricular Function or Very Frail[b,c]
- RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine)
- RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, prednisone)
- RCNOP (rituximab, cyclophosphamide, mitoxantrone, vincristine, prednisone)
- DA-EPOCH[d] (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab
- RCEOP (rituximab, cyclophosphamide, etoposide, vincristine, prednisone)

Patients >80 Years of Age with Comorbidities
- R-mini-CHOP

First-line Consolidation (optional)
- High-dose therapy with autologous stem cell rescue in patients with age-adjusted IPI high-risk disease (category 2B)

Concurrent Presentation with CNS Disease
- Parenchymal: 3 g/m^2 or more of systemic methotrexate given on Day 15 of a 21-day RCHOP cycle that has been supported by growth factors.
- Leptomeningeal: IT methotrexate/cytarabine, consider Ommaya reservoir placement and/or systemic methotrexate (3-3.5 g/m^2)

See Second-line Therapy on BCEL-C 2 of 4.

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

[a]See references for regimens BCEL-C 3 of 4 and BCEL-C 4 of 4.
[b]Inclusion of any anthracycline or anthracenedione in patients with impaired cardiac functioning should have more frequent cardiac monitoring.
[c]There are limited published data regarding the use of these regimens; however, they are used at NCCN Member Institutions for the first-line treatment of DLBCL for patients with poor left ventricular function.
[d]If upward dose adjustment is necessary, doxorubicin should be maintained at base dose and not increased.

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SUGGESTED TREATMENT REGIMENS[a]
(in alphabetical order)

Second-line Therapy[b,e,f] (For patients with intention to proceed to high-dose therapy with autologous stem cell rescue)
- **DHAP (dexamethasone, cisplatin, cytarabine) ± rituximab**
- **ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± rituximab**
- **GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab**
- **GemOx (gemcitabine, oxaliplatin) ± rituximab**
- **ICE (ifosfamide, carboplatin, etoposide) ± rituximab**
- **MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± rituximab**

Second-line Therapy[b,e,f] (non-candidates for high-dose therapy)
- **Bendamustine ± rituximab**
- **CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) ± rituximab - PO and IV**
- **CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± rituximab**
- **DA-EPOCH ± rituximab**
- **GDP ± rituximab**
- **GemOx ± rituximab**
- **Lenalidomide ± rituximab**
- **Rituximab**

See First-line Therapy on **BCEL-C 1 of 4**.

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

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[a] See references for regimens BCEL-C 3 of 4 and BCEL-C 4 of 4.
[b] Inclusion of any anthracycline or anthracenedione in patients with impaired cardiac functioning should have more frequent cardiac monitoring.
[e] If additional anthracycline is administered after a full course of therapy, careful cardiac monitoring is essential. Dexrazoxane may be added as a cardioprotectant.
[f] Rituximab should be included in second-line therapy if there is relapse after a reasonable remission (>6 mo); however; rituximab should often be omitted in patients with primary refractory disease.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS
References

First-line Therapy
CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
+ rituximab with RT
Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-hodgkin's lymphoma. N Engl J Med 1998;339:21-26.
Horning SJ, Weller E, Kim K, et al. Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-hodgkin's lymphoma: Eastern Cooperative Oncology Group Study 1484. J Clin Oncol 2004;22:3032-3038.
Persky DO, Unger JM, Spier CM, et al. Phase II study of rituximab plus three cycles of CHOP and involved-field radiotherapy for patients with limited-stage aggressive B-cell lymphoma: Southwest Oncology Group Study 0014. J Clin Oncol 2008;26:2258-2263.
CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab
Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood 2010;116:2040-2045.
Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 2005;23:4117-4126.
Pfreundschuh M, Trumper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol 2006;7:379-391.

Dose-dense CHOP 14 + rituximab
Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). Lancet Oncol 2008;9:105-116.
Cunningham D, Hawkes EA, Jack A, et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. Lancet 2013;381:1817-1826.
Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab
Purroy N, Lopez A, Vallespi T, Gironella M, Bergua J, Sancho JM. Dose-adjusted EPOCH plus rituximab (DA-EPOCH-R) in untreated patients with poor risk large B-cell lymphoma. A phase 2 study conducted by the Spanish PETHEMA Group [Abstract]. Blood 2009;114:Abstract 2701.
Wilson WH, Dunleavy K, Pittaluga S, et al. Phase II study of dose-adjusted EPOCH and rituximab in untreated diffuse large B-cell lymphoma with analysis of germinal center and post-germinal center biomarkers. J Clin Oncol 2008;26:2717-2724.
Wilson WH, Jung SH, Porcu P, et al. A Cancer and Leukemia Group B multi-center study of DA-EPOCH-rituximab in untreated diffuse large B-cell lymphoma with analysis of outcome by molecular subtype. Haematologica 2012;97:758-765.

First-line Therapy for Patients with Poor Left Ventricular Function
CDOP (cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone) + rituximab
Martino R, Perea G, Caballero MD, et al. Cyclophosphamide, pegylated liposomal doxorubicin (Caelyx), vincristine and prednisone (CCOP) in elderly patients with diffuse large B-cell lymphoma: Results from a prospective phase II study. Haematologica 2002;87:822-827.
Zaja F, Tomadini V, Zaccaria A, et al. CHOP-rituximab with pegylated liposomal doxorubicin for the treatment of elderly patients with diffuse large B-cell lymphoma. Leuk Lymphoma 2006;47:2174-2180.
CNOP (cyclophosphamide, mitoxantrone, vincristine, prednisone) + rituximab
Bessell EM, Burton A, Haynes AP, et al. A randomised multicentre trial of modified CHOP versus MCOP in patients aged 65 years and over with aggressive non-Hodgkin's lymphoma. Ann Oncol 2003;14:258-267.
Bezwoda W, Rastogi RB, Erazo Valla A, et al. Long-term results of a multicentre randomised, comparative phase III trial of CHOP versus CNOP regimens in patients with intermediate- and high-grade non-Hodgkin's lymphomas. Novantrone International Study Group. Eur J Cancer 1995;31A:903-911.
Sonneveld P, de Ridder M, van der Lelie H, et al. Comparison of doxorubicin and mitoxantrone in the treatment of elderly patients with advanced diffuse non-Hodgkin's lymphoma using CHOP versus CNOP chemotherapy. J Clin Oncol 1995;13:2530-2539.
RCEOP (rituximab, cyclophosphamide, etoposide, vincristine, prednisone)
Moccia A, Schaff K, Hoskins P, et al. R-CHOP with etoposide substituted for doxorubicin (R-CEOP): Excellent outcome in diffuse large B cell lymphoma for patients with a contraindication to anthracyclines [abstract]. Blood 2009;114:Abstract 408.

First-line therapy for elderly patients (age >80 years)
R-mini-CHOP
Peyrade F, Jardin F, Thieblemont C, et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. Lancet Oncol 2011;12:460-468.

First-line Consolidation
Stiff PJ, Unger JM, Cook J, et al. Randomized phase III U.S./Canadian intergroup trial (SWOG S9704) comparing CHOP {+/-} R for eight cycles to CHOP {+/-} R for six cycles followed by autotransplant for patients with high-intermediate (H-Int) or high IPI grade diffuse aggressive non-Hodgkin lymphoma (NHL) [abstract]. J Clin Oncol 2011;29: Abstract 8001.

Note: All recommendations are category 2A unless otherwise indicated.
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SUGGESTED TREATMENT REGIMENS
References

<u>Second-line Therapy</u>
Bendamustine ± rituximab
Weidmann E, Kim SZ, Rost A, et al. Bendamustine is effective in relapsed or refractory aggressive non-Hodgkin's lymphoma. Ann Oncol 2002;13:1285-1289.
Vacirca J, Tabbara I, Acs P, Shumaker G. Bendamustine + rituximab as treatment for elderly patients with relapsed or refractory diffuse large B-cell lymphoma [abstract]. Blood 2010;116: Abstract 2806.
Ohmachi K, Niitsu N, Uchida T, et al. Multicenter phase II study of bendamustine plus rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol 2013;31:2103-2109.
DHAP (dexamethasone, cisplatin, cytarabine) ± rituximab
Velasquez WS, Cabanillas F, Salvador P, et al. Effective salvage therapy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone (DHAP). Blood 1988;71:117-122.
Mey UJ, Orlopp KS, Flieger D, et al. Dexamethasone, high-dose cytarabine, and cisplatin in combination with rituximab as salvage treatment for patients with relapsed or refractory aggressive non-Hodgkin's lymphoma. Cancer Invest 2006;24:593-600.
Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 2010;28:4184-4190.
ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± rituximab
Velasquez WS, McLaughlin P, Tucker S, et al. ESHAP - an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. J Clin Oncol 1994;12:1169-1176.
Martin A, Conde E, Arnan M, et al. R-ESHAP as salvage therapy for patients with relapsed or refractory diffuse large B-cell lymphoma: the influence of prior exposure to rituximab on outcome. A GEL/TAMO study. Haematologica 2008;93:1829-1836.
GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab
Crump M, Baetz T, Couban S, et al. Gemcitabine, dexamethasone, and cisplatin in patients with recurrent or refractory aggressive histology B-cell non-Hodgkin lymphoma: a Phase II study by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG). Cancer 2004;101:1835-1842.
GDP (gemcitabine, dexamethasone, carboplatin) ± rituximab
Gopal AK, Press OW, Shustov AR, et al. Efficacy and safety of gemcitabine, carboplatin, dexamethasone, and rituximab in patients with relapsed/refractory lymphoma: a prospective multi-center phase II study by the Puget Sound Oncology Consortium. Leuk Lymphoma 2010;51:1523-1529.
GemOX (gemcitabine, oxaliplatin) + rituximab
Lopez A, Gutierrez A, Palacios A, et al. GEMOX-R regimen is a highly effective salvage regimen in patients with refractory/relapsing diffuse large-cell lymphoma: a phase II study. Eur J Haematol 2008;80:127-132.
ICE (ifosfamide, carboplatin, etoposide) ± rituximab
Zelenetz AD, Hamlin P, Kewalramani T, et al. Ifosfamide, carboplatin, etoposide (ICE)-based second-line chemotherapy for the management of relapsed and refractory aggressive non-Hodgkin's lymphoma. Ann Oncol 2003;14[suppl 1]:i5-10.
Kewalramani T, Zelenetz AD, Nimer SD, et al. Rituximab and ICE (RICE) as second-line therapy prior to autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. Blood 2004;103:3684-8.
Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 2010;28:4184-4190.

Lenalidomide ± rituximab
Witzig TE, Vose JM, Zinzani PL, et al. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. Ann Oncol 2011;22:1622-1627.
Wiernik PH, Lossos IS, Tuscano JM, et al. Lenalidomide monotherapy in relapsed or refractory aggressive Non-Hodgkin's lymphoma. J Clin Oncol 2008;26:4952-4957.
Wang M, Fowler N, Wagner-Bartak N, et al. Oral lenalidomide with rituximab in relapsed or refractory diffuse large cell, follicular, and transformed lymphoma: a phase II clinical trial. Leukemia 2013.
CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) ± rituximab
Chao NJ, Rosenberg SA, and Horning SJ. CEPP(B): An effective and well-tolerated regimen in poor-risk, aggressive non-Hodgkin's lymphoma. Blood 1990;76:1293-1298.
EPOCH + rituximab
Gutierrez M, Chabner BA, Pearson D, et al. Role of a doxorubicin-containing regimen in relapsed and resistant lymphomas: An 8-year follow-up study of EPOCH. J Clin Oncol 2000;18:3633-3642.
Jermann M, Jost LM, Taverna C, et al. Rituximab-EPOCH, an effective salvage therapy for relapsed, refractory or transformed B-cell lymphomas: Results of a phase II study. Ann Oncol 2004;15:511-516.
RGemOx (rituximab, gemcitabine, oxaliplatin)
Corazzelli G, Capobianco G, Arcamone M, et al. Long-term results of gemcitabine plus oxaliplatin with and without rituximab as salvage treatment for transplant-ineligible patients with refractory/relapsing B-cell lymphoma. Cancer Chemother Pharmacol 2009;64:907-916.
El Gnaoui T, Dupuis J, Belhadj K, et al. Rituximab, gemcitabine and oxaliplatin: An effective salvage regimen for patients with relapsed or refractory B-cell lymphoma not candidates for high-dose therapy. Ann Oncol 2007;18:1363-1368.

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DIAGNOSIS[a,b]

ESSENTIAL:
- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis.
- Adequate immunophenotyping to establish diagnosis[c,d,e]
  ‣ IHC panel: CD45 (LCA), CD20, CD3, CD10, Ki-67, BLC2, BCL6, TdT
  or
  ‣ Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD20, CD3, CD5, CD19, CD10, TdT
- Cytogenetics ± FISH: t(8;14) or variants; *MYC*

USEFUL UNDER CERTAIN CIRCUMSTANCES
- FISH: *BCL2*; *BCL6* rearrangements
- EBER-ISH

[a]WHO 2008 classification recognizes that it may not always be possible to distinguish between DLBCL and Burkitt lymphoma. In the setting where it is not possible to distinguish, aggressive therapy per this guideline is appropriate in selected cases. Treatment of double or triple hit tumors is controversial. Optimum regimen has not been identified.

[b]This disease is complex and curable; it is preferred that treatment occur at centers with expertise in the management of the disease.

[c]Typical immunophenotype: sIg+, CD10+, CD20+, TdT-, Ki-67+ (≥95%), BCL2-, BCL6+, simple karyotype with *MYC* rearrangement as sole abnormality.

[d]See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).

WORKUP

ESSENTIAL:
- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC, differential, platelets
- LDH
- Comprehensive metabolic panel
- Uric acid
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Lumbar puncture
- Flow cytometry of cerebrospinal fluid
- Unilateral or bilateral bone marrow biopsy ± aspirate
- HIV testing (if positive, see AIDS-1)
- Hepatitis B testing[f]
- MUGA scan/echocardiogram if anthracycline or anthracenedione-based regimen is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

USEFUL IN SELECTED CASES:
- Neck CT
- Discussion of fertility issues and sperm banking
- Brain MRI
- PET-CT scan[g]

[e]If flow cytometry initially performed, IHC for selected markers (BCL2 and Ki-67) can supplement the flow results.

[f]Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

[g]Initiation of therapy should not be delayed in order to obtain a PET-CT scan.

See Risk Assessment and Induction Therapy (BURK-2)

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RISK ASSESSMENT **INDUCTION THERAPY** **INITIAL RESPONSE** **RELAPSE**

Low risk
- Normal LDH
- Completely resected abdominal lesion or single extra-abdominal mass <10 cm

→ **Clinical trial[h]
or
See Suggested Regimens[i] (BURK-A)**

→ **Complete response[j]** → **Follow-up after complete response:
every 2-3 mo for 1 y,
then every 3 mo for 1 y,
then every 6 mo[k]**

→ **Clinical trial
or
Second-line chemotherapy[i] (BURK-A) followed by HDT/ASCR or allogeneic stem cell transplant in selected patients
or
Best supportive care**

→ **< Complete response[j]**

→ **Clinical trial[h]
or
Individual approach
or
Palliative RT**

Prophylaxis for tumor lysis syndrome is mandatory (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

High risk → **Clinical trial[h]
or
See Suggested Regimens[i] (BURK-A)**

→ **Complete response[j]** → **Observe** → **Follow-up after complete response:
every 2-3 mo for 1 y,
then every 3 mo for 1 y,
then every 6 mo[k]**

or

Consolidation in clinical trial → **Clinical trial
or
Second-line chemotherapy[i] (BURK-A) followed by HDT/ASCR or allogeneic stem cell transplant in selected patients
or
Best supportive care**

→ **< Complete response[j]**

→ **Clinical trial[h]
or
Individual approach
or
Palliative RT**

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[h]Clinical trials may include high-dose therapy with allogeneic or autologous stem cell rescue.
[i]All regimens for Burkitt lymphoma include CNS prophylaxis/therapy.
[j]See Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[k]Relapse after 2 y is rare; therefore, follow-up should be individualized according to patient characteristics.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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Burkitt Lymphoma

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SUGGESTED TREATMENT REGIMENS[a,b]
(in alphabetical order)

Prophylaxis for tumor lysis syndrome is mandatory (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

CHOP is not adequate therapy.

Induction Therapy
Low Risk- Combination Regimens
- CALGB 10002 regimen (cyclophosphamide and prednisone followed by cycles containing either ifosfamide or cyclophosphamide; high-dose methotrexate, leucovorin, vincristine, dexamethasone, and either doxorubicin or etoposide or cytarabine; or intrathecal triple therapy [methotrexate, cytarabine, and hydrocortisone]) + rituximab.
- CODOX-M (original or modified) (cyclophosphamide, doxorubicin, vincristine with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate) ± rituximab (3 cycles)
- Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab (minimum 3 cycles with one additional cycle beyond CR) (regimen includes intrathecal methotrexate) (Data are for patients without CNS disease.)
- HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine + rituximab (regimen includes intrathecal therapy)

High Risk- Combination Regimens
- CALGB 10002 regimen (cyclophosphamide and prednisone followed by cycles containing either ifosfamide or cyclophosphamide; high-dose methotrexate, leucovorin, vincristine, dexamethasone, and either doxorubicin or etoposide or cytarabine; or intrathecal triple therapy [methotrexate, cytarabine, and hydrocortisone] with prophylactic CNS irradiation in select patients) + rituximab
- CODOX-M (original or modified) (cyclophosphamide, doxorubicin, vincristine with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate) alternating with IVAC (ifosfamide, cytarabine, etoposide, and intrathecal methotrexate) ± rituximab
- Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab (for high-risk patients not able to tolerate aggressive treatments) (regimen includes intrathecal methotrexate) (Data are for patients without CNS disease.)
- HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine + rituximab (regimen includes intrathecal therapy)

Second-line Therapy (select patients with reasonable remission)
While no definitive second-line therapies exist, there are limited data for the following regimens:
- Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab (minimum 3 cycles with one additional cycle beyond CR) (regimen includes intrathecal methotrexate) (Data are for patients without CNS disease.)
- RICE (rituximab, ifosfamide, carboplatin, etoposide); intrathecal methotrexate if have not received previously
- RIVAC (rituximab, ifosfamide, cytarabine, etoposide); intrathecal methotrexate if have not received previously
- RGDP (rituximab, gemcitabine, dexamethasone, cisplatin)
- HDAC (high-dose cytarabine)

[a] See references for regimens BURK-A 2 of 2.
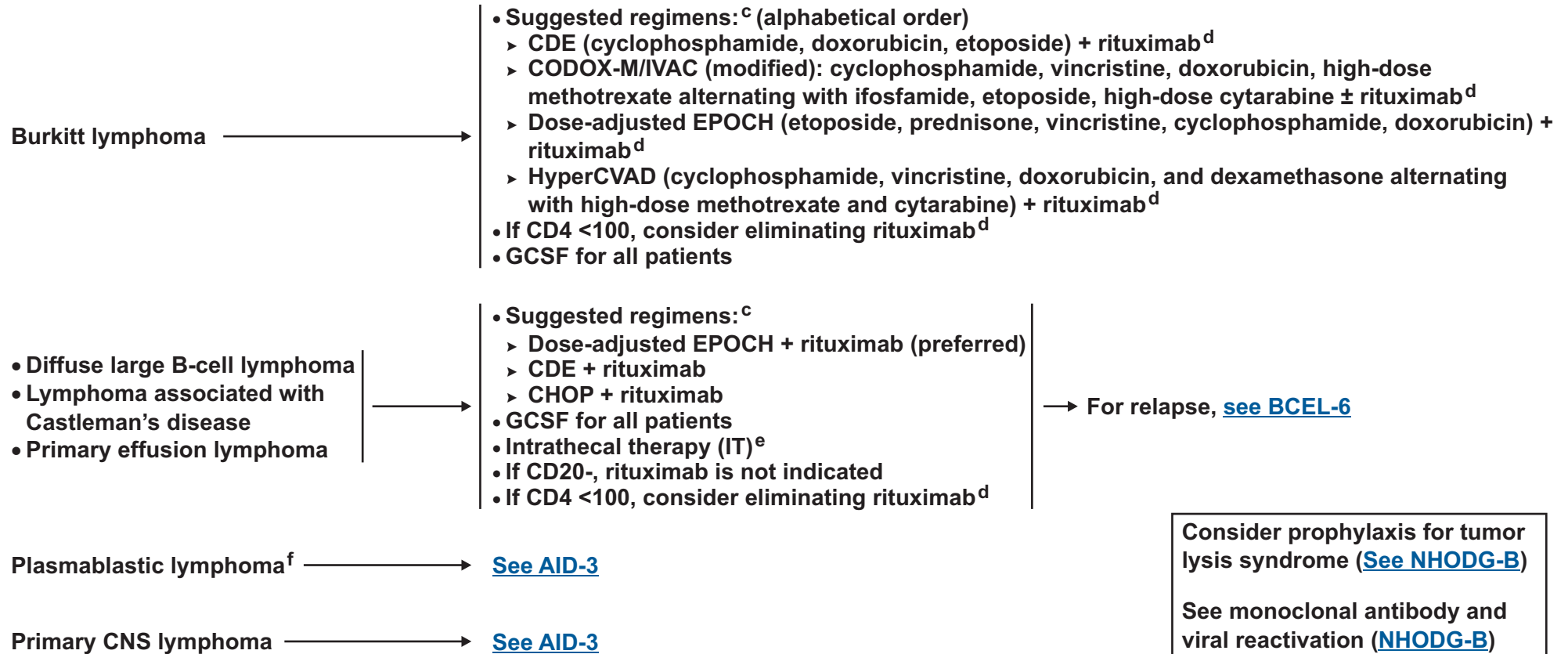[b] All regimens for Burkitt lymphoma include CNS prophylaxis/therapy.

Note: All recommendations are category 2A unless otherwise indicated.
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SUGGESTED TREATMENT REGIMENS
References

Low- and High-Risk Combination Regimens
CALGB 10002
Rizzieri DA, Johnson JL, Byrd JC, et al. Efficacy and toxicity of rituximab and brief duration, high intensity chemotherapy with filgrastim support for Burkitt or Burkitt-like leukemia/lymphoma: Cancer and Leukemia Group B (CALGB) Study 10002 [abstract]. Blood 2010;116:Abstract 858.

CODOX-M (original or modified) (cyclophosphamide, doxorubicin, vincristine with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate) with (for high-risk) or without (for low-risk) alternating IVAC (ifosfamide, cytarabine, etoposide, and intrathecal methotrexate ± rituximab)
LaCasce A, Howard O, Lib S, et al. Modified magrath regimens for adults with Burkitt and Burkitt-like lymphoma: preserved efficacy with decreased toxicity. Leuk Lymphoma 2004;45:761-767.
Mead GM, Sydes MR, Walewski J, et al. An international evaluation of CODOX-M and CODOX-M alternating with IVAC in adult Burkitt's lymphoma: results of United Kingdom Lymphoma Group LY06 study. Ann Oncol 2002;13:1264-1274.
Barnes JA, Lacasce AS, Feng Y, et al. Evaluation of the addition of rituximab to CODOX-M/IVAC for Burkitt's lymphoma: a retrospective analysis. Ann Oncol 2011;22:1859-1864.

Dose-adjusted EPOCH plus rituximab (regimen includes IT methotrexate)
Dunleavy K, Pittaluga S, Wayne AS, et al. MYC+ aggressive B-cell lymphomas: A novel therapy of untreated Burkitt lymphoma (BL) and MYC+ diffuse large B-cell lymphoma (DLBCL) with DA-EPOCH-R [abstract]. Ann Oncol 2011;22 (Supple 4): Abstract 71.

HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine + rituximab
Thomas DA, Faderl S, O'Brien S, Bueso-Ramos C, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer 2006;106:1569-1580.
Thomas DA, Kantarjian HM, Cortes J, et al. Long-term outcome after hyper-CVAD and rituximab chemoimmunotherapy for Burkitt (BL) or Burkitt-like (BLL) leukemia/lymphoma and mature B-cell acute lymphocytic leukemia (ALL) [abstract]. Blood 2008;112:Abstract 1929.

Second-line Therapy
RICE (rituximab, ifosfamide, carboplatin, etoposide)
Griffin TC, Weitzman S, Weinstein H, et al. A study of rituximab and ifosfamide, carboplatin, and etoposide chemotherapy in children with recurrent/refractory B-cell (CD20+) non-Hodgkin lymphoma and mature B-cell acute lymphoblastic leukemia: A report from the Children's Oncology Group. Pediatr Blood Cancer 2009;52:177-181.

Note: All recommendations are category 2A unless otherwise indicated.
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Lymphoblastic Lymphoma[a]

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DIAGNOSIS[b]

ESSENTIAL:

- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis.
- Adequate immunophenotyping to establish diagnosis[c]
  - ➤ IHC panel: CD45 (LCA), CD19, CD20, CD79a, CD3, CD2, CD5, CD7, TdT, CD1a, CD10, cyclin D1
    or
  - ➤ Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD3, CD5, CD4, CD7, CD8, CD19, CD20, CD10, TdT, CD13, CD33, CD1a, cytoplasmic CD3, CD22, myeloperoxidase
- Cytogenetics ± FISH: *MYC*; t(9;22); t(8;14), and variants or PCR for *BCR-ABL*

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Additional immunohistochemical studies to establish lymphoma subtype
  - ➤ Paraffin panel: CD22, CD4, CD8, cyclin D1
- Molecular analysis to detect: antigen receptor gene rearrangements

WORKUP

ESSENTIAL:

- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC, differential, platelets
- LDH
- Comprehensive metabolic panel
- Uric acid, phosphate
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Lumbar puncture
- Flow cytometry of cerebrospinal fluid
- Bilateral or unilateral bone marrow biopsy ± aspirate with flow and cytogenetics
- Hepatitis B testing[d]
- MUGA scan/echocardiogram if anthracycline or anthracenedione-based regimen is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

USEFUL IN SELECTED CASES:
- Head MRI
- Discussion of fertility issues and sperm banking
- Beta-2-microglobulin
- PET-CT scan[e]

See NCCN Guidelines for Acute Lymphoblastic Leukemia

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[a] The lymphoblastic lymphoma (LL) category comprises two diseases, T-cell LL (LL-T;90%) and B-cell LL (LL-B;10%), which corresponds to T-ALL and B-ALL, respectively, with presentations in extramedullary sites.

[b] This disease is complex and curable; it is preferred that treatment occur at centers with expertise in the management of the disease.

[c] Typical immunophenotype: <u>LL-B</u>: sIg-, CD10+/-, CD19+, CD20-/+, TdT+.
<u>LL-T</u>: sIg-, CD10-, CD19/20-, CD3-/+, CD4/8+/+, CD1a+/-, TdT+, CD2+, CD7+ cytoplasmic CD3+, sCD3-/+.

[d] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

[e] Initiation of therapy should not be delayed in order to obtain a PET-CT scan.

Note: All recommendations are category 2A unless otherwise indicated.
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DIAGNOSIS

ESSENTIAL:
- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis.
- Adequate immunophenotyping to establish diagnosis[a]
  - ➤ IHC panel: CD45 (LCA), CD20, CD3, CD10, BCL2, BCL6, Ki-67, CD138, kappa/lambda, HHV8
    or
  - ➤ Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD3, CD5, CD19, CD10, CD20
- Epstein-Barr virus in situ hybridization (EBER-ISH)

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- Additional immunohistochemical studies to establish lymphoma subtype
  - ➤ DLBCL, Burkitt, Plasmablastic, Primary effusion lymphoma (PEL):
    CD10, BCL2, Ki-67, BCL6, CD138, CD30 for PEL
- Molecular analysis to detect: antigen receptor gene rearrangements; *BCL2*; *BCL6*; *MYC* rearrangements
- Cytogenetics or FISH: *BCL2*; *BCL6*; *MYC*

WORKUP

ESSENTIAL
- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC, differential, platelets
- LDH
- Comprehensive metabolic panel
- Uric acid, phosphate
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- PET-CT scan
- Bone marrow biopsy ± aspirate
- CD4 count
- LP
- HIV viral load
- Hepatitis B testing[b]
- MUGA scan/echocardiogram if anthracycline or anthracenedione-based regimen is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

USEFUL IN SELECTED CASES:
- UGI/barium enema/endoscopy
- Neck CT
- Plain bone radiographs and bone scan
- Discussion of fertility issues and sperm banking
- Beta-2-microglobulin
- Brain MRI with gadolinium, or head CT
- EBV viral load

→ See Treatment
(AIDS-2) and
(AIDS-3)

[a]See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).
[b]Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

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TREATMENT

Antiretrovirals can be administered safely with chemotherapy; however, some regimens have recommended discontinuation. Any change in antiviral therapy should be done in consultation with an infectious disease specialist.

Burkitt lymphoma

- Suggested regimens:[c] (alphabetical order)
  ➤ CDE (cyclophosphamide, doxorubicin, etoposide) + rituximab[d]
  ➤ CODOX-M/IVAC (modified): cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate alternating with ifosfamide, etoposide, high-dose cytarabine ± rituximab[d]
  ➤ Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab[d]
  ➤ HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab[d]
- If CD4 <100, consider eliminating rituximab[d]
- GCSF for all patients

- Diffuse large B-cell lymphoma
- Lymphoma associated with Castleman's disease
- Primary effusion lymphoma

- Suggested regimens:[c]
  ➤ Dose-adjusted EPOCH + rituximab (preferred)
  ➤ CDE + rituximab
  ➤ CHOP + rituximab
- GCSF for all patients
- Intrathecal therapy (IT)[e]
- If CD20-, rituximab is not indicated
- If CD4 <100, consider eliminating rituximab[d]

→ For relapse, see BCEL-6

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

Plasmablastic lymphoma[f] ⟶ See AID-3

Primary CNS lymphoma ⟶ See AID-3

[c]See references for regimens (AIDS-A).
[d]In patients on active antiretrovirals treated with rituximab-based regimens, low CD4 count (<100/mcL) may be associated with decreased response and survival outcomes; CD4 count <50/mcL has been associated with increased treatment-related deaths.
[e]Prophylactic IT methotrexate is used at some NCCN Institutions for all patients with HIV-associated DLBCL. At other NCCN Institutions, patients receive IT methotrexate in selective settings (paranasal sinus, testicular, epidural, bone marrow with large cell lymphoma, EBER positivity, or ≥2 extranodal sites and elevated LDH).

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TREATMENT

Antiretrovirals can be administered safely with chemotherapy; however, some regimens have recommended discontinuation. Any change in antiviral therapy should be done in consultation with an infectious disease specialist.

Plasmablastic lymphoma[f]

- Suggested regimens:[c]
  ➤ CODOX-M/IVAC (modified)
  ➤ Dose-adjusted EPOCH
  ➤ HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine)
- Standard CHOP is not adequate therapy

Primary CNS lymphoma

- Consider high-dose methotrexate
- Consider RT alone
- For select patients with good performance status on HAART, see NCCN Guidelines for CNS- Primary CNS Lymphoma
- Best supportive care (See NCCN Guidelines for Palliative Care)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

[c]See references for regimens (AIDS-A).
[f]Management can also apply to HIV-negative plasmablastic lymphoma.

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SUGGESTED TREATMENT REGIMENS
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CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate alternating with ifosfamide, etoposide, high-dose cytarabine) ± rituximab

Wang ES, Straus DJ, Teruya-Feldstein J, et al. Intensive chemotherapy with cyclophosphamide, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine (CODOX-M/IVAC) for human immunodeficiency virus-associated Burkitt lymphoma. Cancer 2003;98:1196-1205.

Barnes JA, LaCasce AS, Feng Y, et al. Evaluation of the addition of rituximab to CODOX-M/IVAC for Burkitt's lymphoma: A retrospective analysis. Ann Oncol 2011; 22:1859-1864.

Noy A, Kaplan L, Lee J, et al. Modified dose intensive R- CODOX-M/IVAC for HIV-associated Burkitt (BL) (AMC 048) shows efficacy and tolerability, and predictive potential of IRF4/MUM1 expression. Infectious Agents and Cancer 2012;7:O14.

Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)

Little RF, Pittaluga S, Grant N, et al. Highly effective treatment of acquired immunodeficiency syndrome-related lymphoma with dose-adjusted EPOCH: impact of antiretroviral therapy suspension and tumor biology. Blood 2003;101:4653-4659.

Dose-adjusted EPOCH + rituximab

Barta SK, Lee JY, Kaplan LD, et al. Pooled analysis of AIDS malignancy consortium trials evaluating rituximab plus CHOP or infusional EPOCH chemotherapy in HIV-associated non-Hodgkin lymphoma. Cancer 2012;118:3977-3983.

Bayraktar UD, Ramos JC, Petrich A, et al. Outcome of patients with relapsed/refractory acquired immune deficiency syndrome-related lymphoma diagnosed 1999-2008 and treated with curative intent in the AIDS Malignancy Consortium. Leuk Lymphoma 2012;53:2383-2389.

CDE (cyclophosphamide, doxorubicin, and etoposide)

Sparano JA, Lee S, Chen MG, et al. Phase II trial of infusional cyclophosphamide, doxorubicin, and etoposide in patients with HIV-associated non-Hodgkin's Lymphoma: An Eastern Cooperative Oncology Group Trial (E1494). J Clin Oncol 2004;22:1491-1500.

CDE + rituximab

Spina M, Jaeger U, Sparano JA, et al. Rituximab plus infusional cyclophosphamide, doxorubicin, and etoposide in HIV-associated non-Hodgkin lymphoma: Pooled results from 3 phase 2 trials. Blood 2005;105:1891-1897.

Spina M, Simonelli C, Vaccher E, et al. Long-term follow-up of rituximab and infusional cyclophosphamide, doxorubicin, and etoposide (CDE) in combination with HAART in HIV related Non-Hodgkin's Lymphomas (NHL). Blood 2008;112:Abstract 1467.

HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) ± rituximab

Cortes J, Thomas D, Rios A, et al. Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone and highly active antiretroviral therapy for patients with acquired immunodeficiency syndrome-related Burkitt lymphoma/leukemia. Cancer 2002;94:1492-1499.

Thomas DA, Faderl S, O'Brien S, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer 2006;106:1569-1580.

Thomas DA, Kantarjian HM, Cortes J, et al. Long-term outcome after hyper-CVAD and rituximab chemoimmunotherapy for Burkitt (BL) or Burkitt-like (BLL) leukemia/lymphoma and mature B-cell acute lymphocytic leukemia (ALL) [abstract]. Blood 2008;112:Abstract 1929.

CHOP + rituximab

Boue F, Gabarre J, Gisselbrecht C, et al. Phase II trial of CHOP plus rituximab in patients with HIV-associated non-Hodgkin's lymphoma. J Clin Oncol 2006;24:4123-4128.

Ribera JM, Oriol A, Morgades M, et al. Safety and efficacy of cyclophosphamide, adriamycin, vincristine, prednisone and rituximab in patients with human immunodeficiency virus-associated diffuse large B-cell lymphoma: results of a phase II trial. Br J Haematol 2008;140:411-419.

Rituximab and CD4 counts

Sparano JA, Lee JY, Kaplan LD et al. Rituximab plus concurrent infusional EPOCH chemotherapy is highly effective in HIV-associated B-cell non-Hodgkin lymphoma. Blood 2010;115:3008-3016.

Kaplan LD, Lee JY, Ambinder RF, et al. Rituximab does not improve clinical outcome in a randomized phase 3 trial of CHOP with or without rituximab in patients with HIV-associated non-Hodgkin lymphoma: AIDS-Malignancies Consortium Trial 010. Blood 2005;106:1538-1543.

Barta SK, Xue X, Tamari R, et al. A pooled analysis of 1,144 patients with HIV-associated lymphoma: Assessment of lymphoma-, HIV-, and treatment-specific factors on clinical outcomes [abstract]. J Clin Oncol 2012;30:Abstract 8005.

Barta SK, Lee JY, Kaplan LD, et al. Pooled analysis of AIDS malignancy consortium trials evaluating rituximab plus CHOP or infusional EPOCH chemotherapy in HIV-associated non-Hodgkin lymphoma. Cancer 2012;118:3977-3983.

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Primary Cutaneous B-Cell Lymphomas[a]

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DIAGNOSIS

ESSENTIAL:
- Review of all slides with at least one paraffin block representative of the tumor should be done by a pathologist with expertise in the diagnosis of primary cutaneous B-cell lymphoma. Rebiopsy if consult material is nondiagnostic.
- Histopathology review of adequate biopsy (punch, incisional, excisional).
- Adequate immunophenotyping to establish diagnosis [b,c]
  - IHC panel: CD20, CD3, CD5, CD10, BCL2, BCL6, IRF4/MUM1

USEFUL IN CERTAIN CIRCUMSTANCES:
- Additional immunohistochemical studies to establish lymphoma subtype
  - IHC panel: Ki-67, CD43, CD21, CD23
  - Cyclin D1, kappa/lambda
  - Assessment of IgM and IgD expression (to further help in distinguishing PC-DLBCL, leg type from PCFCL)
- Cytogenetics or FISH: t(14;18)
- If adequate biopsy material available, flow cytometry or PCR can be useful in determining B-cell clonality.

WORKUP

ESSENTIAL:[d]
- History and physical exam, including complete skin exam
- CBC, differential, comprehensive metabolic panel
- LDH
- Hepatitis B testing[e] if rituximab considered
- Chest/abdominal/pelvic CT
- Bone marrow biopsy, if PC-DLBCL, Leg type
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

USEFUL IN SELECTED CASES:
- PET-CT scan
- Bone marrow biopsy
  - Consider if PCFCL
  - Optional if PCMZL
- Peripheral blood flow cytometry, if CBC demonstrates lymphocytosis
- SPEP/quantitative immunoglobulins for PCMZL

PCMZL: Primary Cutaneous Marginal Zone Lymphoma
PCFCL: Primary Cutaneous Follicle Center Lymphoma
PC-DLBCL, Leg type: Primary Cutaneous Diffuse Large B-cell Lymphoma, Leg type

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See Initial Therapy for Primary Cutaneous Marginal Zone Lymphoma (CUTB-2)

See Initial Therapy for Primary Cutaneous Follicle Center Lymphoma (CUTB-2)

See Initial Therapy for Primary Cutaneous Diffuse Large B-cell Lymphoma, Leg Type (CUTB-4)

NOTE: A germinal (or follicle) center phenotype and large cells in a skin lesion is _not_ equivalent to DLBCL but is consistent with primary cutaneous germinal/follicle center lymphoma.

[a] For non-cutaneous, see Nongastric MALT Lymphoma (NGMLT-1).
[b] See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).
[c] Typical immunophenotype: PC-DLBCL: CD20+ BCL2+ CD10- BCL6+/- IRF4/MUM1+/- ; PCFCL: CD20+ BCL2- CD10-/+ BCL6+ IRF4/MUM1-; PCMZL: CD20+ BCL2+/- CD10- BCL6- IRF4/MUM1+/- cytoplasmic kappa+ or lambda+ in about 40%.

[d] Rule out drug-induced cutaneous lymphoid hyperplasia.
[e] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

Note: All recommendations are category 2A unless otherwise indicated.
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PRIMARY CUTANEOUS MARGINAL ZONE LYMPHOMA OR FOLLICLE CENTER LYMPHOMA[f]

STAGE[g] | **INITIAL THERAPY[h]** | **SECONDARY THERAPY**

Solitary/regional, T1-2 (Ann Arbor Stage IE)

Local RT (preferred)
or
Excision

In selected cases:
Observation[i]
or
Topicals[j]
or
Intralesional steroids

→ CR/PR → Persistent or progressive disease

→ Regional → Observation or Excision or Topicals[j] or Injected steroids or Local RT → Relapsed disease, See CUTB-3

→ Generalized disease (extracutaneous disease) → Manage as per FOLL-3

→ Generalized disease (skin only)

Generalized disease (skin only), T3

Observation
or
Rituximab
or
Topicals[j]
or
Local RT for palliation of symptoms
or
Intralesional steroids
or
Palliative chemotherapy[k] such as chlorambucil ± rituximab or CVP ± rituximab

→ CR/PR → Persistent or progressive disease → Relapsed disease, See CUTB-3

Extracutaneous disease → Manage as per FOLL-3

See monoclonal antibody and viral reactivation (NHODG-B)

[f]Unless clinically indicated, additional imaging studies during the course of treatment are not needed.

[g]See TNM Classification of Cutaneous Lymphoma other than MF/SS (CUTB-A).

[h]See Treatment References (CUTB-B).

[i]When RT or surgical treatment is neither feasible nor desired.

[j]There are case reports showing efficacy of topicals, which include steroids, imiquimod, nitrogen mustard, and bexarotene.

[k]In rare circumstances for very extensive disease, other combination chemotherapy regimens listed in FOLL-B are used.

Note: All recommendations are category 2A unless otherwise indicated.
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PRIMARY CUTANEOUS MARGINAL ZONE LYMPHOMA OR FOLLICLE CENTER LYMPHOMA[f]

RELAPSED DISEASE   **STAGE[g]**   **ADDITIONAL THERAPY[h]**

Relapsed disease

→ **Solitary/regional, T1-2 (Ann Arbor Stage IE)** →
Observation
or
Excision
or
Topicals[j]
or
Intralesional steroids
or
Local RT
→ CR/PR → **Persistent or progressive disease** →
- Regional → **Generalized disease (extracutaneous disease)** → **Manage as per FOLL-3**
- **Generalized disease (skin only)**

→ Refractory[l] →

→ **Generalized disease (skin only), T3** →
Observation
or
Rituximab
or
Topicals[j]
or
Local RT for palliation of symptoms
or
Intralesional steroids
or
Palliative chemotherapy[k] such as chlorambucil ± rituximab or CVP ± rituximab
→ CR/PR → **Persistent or progressive disease**
→ Refractory[l] → **Manage as per FOLL-3**

→ **Extracutaneous disease** → **Manage as per FOLL-3**

See monoclonal antibody and viral reactivation (NHODG-B)

[f]Unless clinically indicated, additional imaging studies during the course of treatment is not needed.
[g]See TNM Classification of Cutaneous Lymphoma other than MF/SS (CUTB-A).
[h]See Treatment References (CUTB-B).

[j]There are case reports showing efficacy of topicals, which include steroids, imiquimod, nitrogen mustard, and bexarotene.
[k]In rare circumstances for very extensive disease, other combination chemotherapy regimens listed in FOLL-B are used.
[l]Refractory to all previous treatments.

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PRIMARY CUTANEOUS DIFFUSE LARGE B-CELL LYMPHOMA, LEG TYPE

STAGE[g]	INITIAL THERAPY			SECONDARY THERAPY

Solitary regional, T1-2 (Ann Arbor Stage IE) →

RCHOP[m] + local RT
or
Local RT[n]
or
Clinical trial

→ CR → Observe → Relapse →

PR →

RCHOP (if not previously received)
or
Manage as per BCEL-6
or
Local RT to previously unirradiated tumor

Generalized disease (skin only), T3 →

RCHOP[m] ± local RT
or
Clinical trial

→ CR → Observe → Relapse →

PR →

Manage as per BCEL-6
or
Local RT for palliation
or
Radioimmunotherapy

Extracutaneous disease → Manage as per BCEL-3

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

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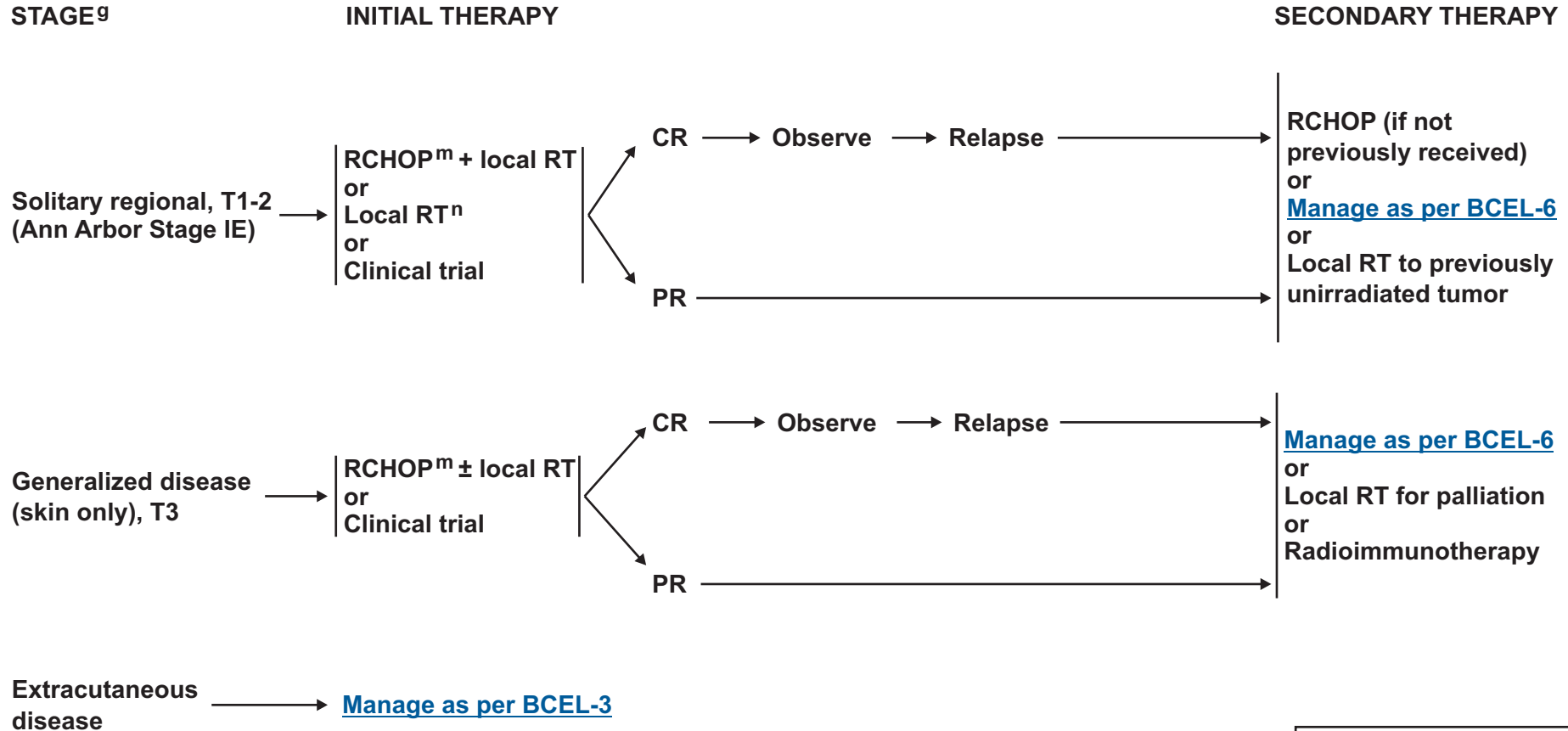
[g] See TNM Classification of Cutaneous Lymphoma other than MF/SS (CUTB-A).
[m] For patients who cannot tolerate anthracyclines, see BCEL-C for regimens for patients with poor left ventricular function.
[n] For patients not able to tolerate chemotherapy.

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TNM CLASSIFICATION OF CUTANEOUS LYMPHOMA OTHER THAN MF/SS[a,b]

T	
T1	**Solitary skin involvement**
	T1a: a solitary lesion <5 cm diameter
	T1b: a solitary >5 cm diameter
T2	**Regional skin involvement: multiple lesions limited to 1 body region or 2 contiguous body regions[b]**
	T2a: all-disease-encompassing in a <15-cm-diameter circular area
	T2b: all-disease-encompassing in a >15- and <30-cm-diameter circular area
	T2c: all-disease-encompassing in a >30-cm-diameter circular area
T3	**Generalized skin involvement**
	T3a: multiple lesions involving 2 noncontiguous body regions[b]
	T3b: multiple lesions involving ≥3 body regions[b]

N	
N0	**No clinical or pathologic lymph node involvement**
N1	**Involvement of 1 peripheral lymph node region[c] that drains an area of current or prior skin involvement**
N2	**Involvement of 2 or more peripheral lymph node regions[c] or involvement of any lymph node region that does not drain an area of current or prior skin involvement**
N3	**Involvement of central lymph nodes**

M	
M0	**No evidence of extracutaneous non–lymph node disease**
M1	**Extracutaneous non-lymph node disease present**

[a] This work was originally published in Blood. Kim YH, Willemze R, Pimpinell Ni, et al, for the ISCL and the EORTC. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome: A proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC) Blood 2007;110:479-484. © The American Society of Hematology.

[b] For definition of body regions, see Body Regions for the Designation of T (Skin Involvement) Category (CUTB-A 2 of 2).

[c] Definition of lymph node regions is consistent with the Ann Arbor system: Peripheral sites: antecubital, cervical, supraclavicular, axillary, inguinal-femoral, and popliteal. Central sites: mediastinal, pulmonary hilar, paraortic, and iliac.

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BODY REGIONS FOR THE DESIGNATION OF T (SKIN INVOLVEMENT) CATEGORY[a,b,c]

HN	Head & Neck
C	Chest
LUA	Left Upper Arm
LLAH	Left Lower Arm & Hand
AG	Abdominal & Genital
LUL	Left Upper Leg
LLLF	Left Lower Leg & Feet
RUA	Right Upper Arm
RLAH	Right Lower Arm & Hand
RUL	Right Upper Leg
RLLF	Right Lower Leg & Feet
UB	Upper Back
LBB	Lower Back & Buttock
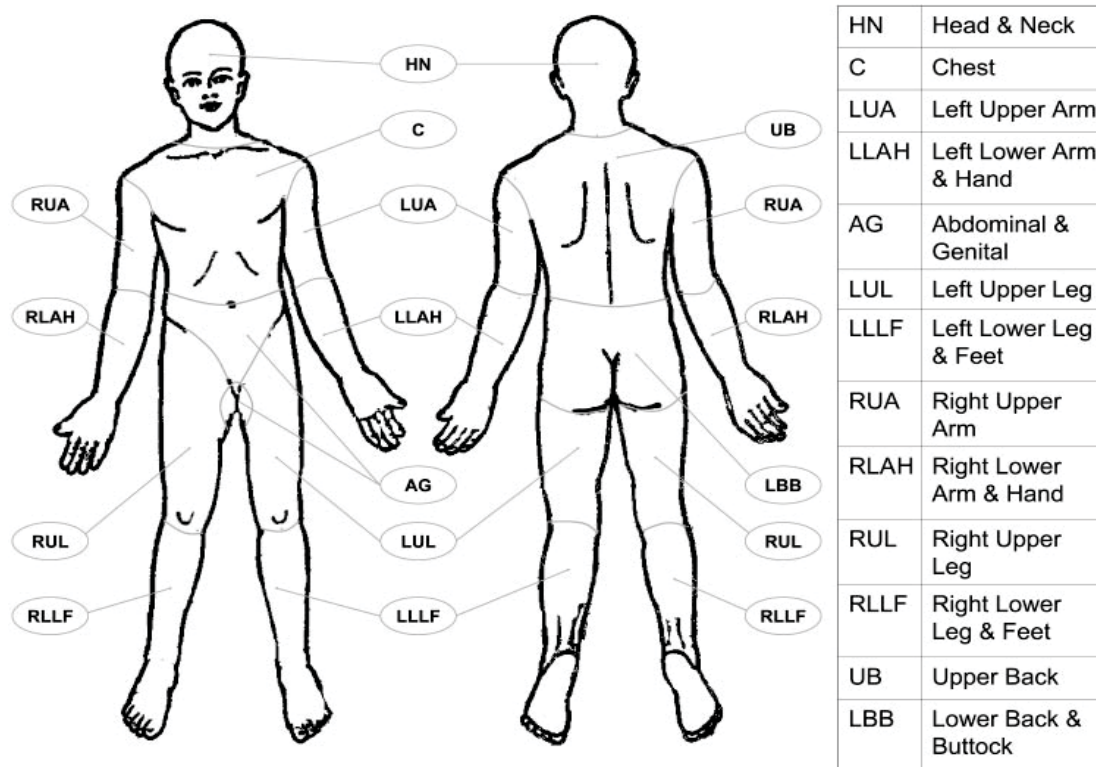
[a] Kim YH, Willemze R, Pimpinell Ni, et al, for the ISCL and the EORTC. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome: A proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110:479-484.

[b] Left and right extremities are assessed as separate body regions. The designation of these body regions are based on regional lymph node drainage patterns.

[c] Definition of body regions: Head and neck: inferior border—superior border of clavicles, T1 spinous process. Chest: superior border—superior border of clavicles; inferior border—inferior margin of rib cage; lateral borders—midaxillary lines, glenohumeral joints (inclusive of axillae). Abdomen/genital: superior border—inferior margin of rib cage; inferior border—inguinal folds, anterior perineum; lateral borders—mid-axillary lines. Upper back: superior border—T1 spinous process; inferior border—inferior margin of rib cage; lateral borders—mid-axillary lines. Lower back/buttocks: superior border—inferior margin of rib cage; inferior border—inferior gluteal fold, anterior perineum (inclusive of perineum); lateral borders—midaxillary lines. Each upper arm: superior borders—glenohumeral joints (exclusive of axillae); inferior borders—ulnar/radial-humeral (elbow) joint. Each lower arm/hand: superior borders—ulnar/radial-humeral (elbow) joint. Each upper leg (thigh): superior borders—inguinal folds, inferior gluteal folds; inferior borders—mid-patellae, midpopliteal fossae. Each lower leg/foot: superior borders—mid-patellae, mid-popliteal fossae.

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TREATMENT REFERENCES

Rituximab

Morales AV, Advani R, Horwitz SM, et al. Indolent primary cutaneous B-cell lymphoma: experience using systemic rituximab. J Am Acad Dermatol 2008;59:953-957.

Heinzerling LM, Urbanek M, Funk JO, et al. Reduction of tumor burden and stabilization of disease by systemic therapy with anti-CD20 antibody (rituximab) in patients with primary cutaneous B-cell lymphoma. Cancer 2000;89:1835-1844.

Valencak J, Weihsengruber F, Rappersberger K, et al. Rituximab monotherapy for primary cutaneous B-cell lymphoma: Response and follow-up in 16 patients. Ann Oncol 2009;20:326-330.

Senff NJ, Noordijk EM, Kim YH, et al. European Organization for Research and Treatment of Cancer and International Society for Cutaneous Lymphoma consensus recommendations for the management of cutaneous B-cell lymphomas. Blood 2008;112:1600-1609.

Heinzerling L, Dummer R, Kempf W, Schmid MH, Burg G. Intralesional therapy with anti-CD20 monoclonal antibody rituximab in primary cutaneous B-cell lymphoma. Arch Dermatol 2000;136:374-378.

Topicals

Topical/intralesional corticosteroids

Bekkenk MW, Vermeer MH, Geerts ML, et al. Treatment of multifocal primary cutaneous B-cell lymphoma: a clinical follow-up study of 29 patients. J Clin Oncol 1999;17:2471-2478.

Perry A, Vincent BJ, Parker SR. Intralesional corticosteroid therapy for primary cutaneous B-cell lymphoma. Br J Dermatol 2010;163:223-225.

Topical nitrogen mustard

Bachmeyer C, Orlandini V, Aractingi S. Topical mechlorethamine and clobetasol in multifocal primary cutaneous marginal zone-B cell lymphoma. British Journal of Dermatology 2006;154:1207-1209.

Topical bexarotene

Trent JT, Romanelli P, Kerdel FA. Topical Targretin and Intralesional Interferon Alfa for Cutaneous Lymphoma of the Scalp. Arch Dermatol 2002;138:1421-1423.

Topical imiquimod

Coors EA, Schuler G, Von Den Driesch P. Topical imiquimod as treatment for different kinds of cutaneous lymphoma. Eur J Dermatol 2006;16:391-393.

Stavrakoglou A, Brown VL, Coutts I. Successful treatment of primary cutaneous follicle centre lymphoma with topical 5% imiquimod. Br J Dermatol 2007;157:620-622.

Chemotherapy

Hoefnagel JJ, Vermeer MH, Jansen PM, et al. Primary cutaneous marginal zone B-cell lymphoma: Clinical and therapeutic features in 50 cases. Arch Dermatol 2005;141:1139-1145.

Bekkenk MW, Vermeer MH, Geerts ML, et al. Treatment of multifocal primary cutaneous B-cell lymphoma: a clinical follow-up study of 29 patients. J Clin Oncol 1999;17:2471-2478.

Senff NJ, Noordijk EM, Kim YH, et al. European Organization for Research and Treatment of Cancer and International Society for Cutaneous Lymphoma consensus recommendations for the management of cutaneous B-cell lymphomas. Blood 2008;112:1600-1609.

Grange F, Beylot-Barry M, Courville P, et al. Primary cutaneous diffuse large B-cell lymphoma, leg type: clinicopathologic features and prognostic analysis in 60 cases. Arch Dermatol 2007;143:1144-1150.

Brice P, Cazals D, Mounier N, et al. Primary cutaneous large-cell lymphoma: analysis of 49 patients included in the LNH87 prospective trial of polychemotherapy for high-grade lymphomas. Groupe d'Etude des Lymphomes de l'Adulte. Leukemia 1998;12:213-219.

Rijlaarsdam JU, Toonstra J, Meijer OW, Noordijk EM, Willemze R. Treatment of primary cutaneous B-cell lymphomas of follicle center cell origin: A clinical follow-up study of 55 patients treated with radiotherapy or polychemotherapy. J Clin Oncol 1996;14:549-555.

Vermeer MH, Geelen FA, van Haselen CW, et al. Primary cutaneous large B-cell lymphomas of the legs. A distinct type of cutaneous B-cell lymphoma with an intermediate prognosis. Dutch Cutaneous Lymphoma Working Group. Arch Dermatol 1996;132:1304-1308.

Palliative low-dose RT

Neelis KJ, Schimmel EC, Vermeer MH, et al. Low-dose palliative radiotherapy for cutaneous B- and T-cell lymphomas. Int J Radiat Oncol Biol Phys 2009;74:154-158.

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DIAGNOSIS

SUBTYPES

ESSENTIAL:
- **Review of all slides with at least one paraffin block representative of the tumor should be done by a hematopathologist with expertise in the diagnosis of PTCL. Rebiopsy if consult material is nondiagnostic.**
- **An FNA alone is not sufficient for the initial diagnosis of peripheral T-cell lymphoma.**
- **Adequate immunophenotyping to establish diagnosis[a,b]**
  - ➤ **IHC panel: CD20, CD3, CD10, BCL6, Ki-67, CD5, CD30, CD2, CD4, CD8, CD7, CD56, CD57 CD21, CD23, EBER-ISH, ALK or**
  - ➤ **Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD3, CD5, CD19, CD10, CD20, CD30, CD4, CD8, CD7, CD2; TCRαβ; TCRγ**

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- **Molecular analysis to detect: antigen receptor gene rearrangements; t(2;5) and variants**
- **Additional immunohistochemical studies to establish lymphoma subtype: βF1, TCR-CγM1, CD279/PD1, CXCL-13**
- **Cytogenetics to establish clonality**
- **Assessment of HTLV-1[c] serology in at-risk populations. HTLV-1 PCR if serology is indeterminate.**

Subtypes included:
- **Peripheral T-cell lymphoma (PTCL), NOS**
- **Angioimmunoblastic T-cell lymphoma (AITL)[d]**
- **Anaplastic large cell lymphoma (ALCL), ALK positive**
- **ALCL, ALK negative**
- **Enteropathy-associated T-cell lymphoma (EATL)**

Subtypes *not* included:
- **Primary cutaneous ALCL**
- **All other T-cell lymphomas**

Extranodal NK/T-cell lymphoma, nasal type (See NKTL-1)

→ **See Workup (TCEL-2)**

[a]Molecular diagnosis for T-cell receptor rearrangements should be done in most circumstances to confirm clonality. T-cell receptor rearrangements alone are not sufficient for diagnosis, as these are often seen with reactive/inflammatory processes.
[b]See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).
[c]See map for prevalence of HTLV-1 by geographic region.
[d]AITL may occasionally present with concurrent DLBCL. EBV and appropriate immunohistochemistry should be performed.

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WORKUP

ESSENTIAL:[e]
- **Physical exam; full skin exam; attention to node-bearing areas, including Waldeyer's ring; evaluation of size of liver and spleen, nasopharynx**
- **Performance status**
- **B symptoms**
- **CBC, differential, platelets**
- **Bone marrow biopsy**
- **LDH**
- **Comprehensive metabolic panel**
- **Uric acid**
- **Chest/abdominal/pelvic CT with contrast of diagnostic quality and/or PET-CT scan**
- **Calculation of International Prognostic Index (IPI)**[f]
- **MUGA scan/echocardiogram if anthracycline or anthracenedione-based regimen is indicated**
- **Pregnancy testing in women of child-bearing age (if chemotherapy planned)**

USEFUL IN SELECTED CASES:
- **Neck CT**
- **Head CT or MRI**
- **Skin biopsy**
- **Discussion of fertility issues and sperm banking**
- **HIV testing**

→ **See Induction Therapy (TCEL-3)**

[e]The role of intrathecal prophylaxis in PTCL is largely unknown.
[f]See International Prognostic Index (TCEL-A).

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| STAGE | INDUCTION THERAPY | Consider prophylaxis for tumor lysis syndrome (See NHODG-B) |

ALCL, ALK +

Stage I, II → Multiagent chemotherapy[h] x 6 cycles ± RT (30-40 Gy to involved region) **or** Multiagent chemotherapy[h] x 3-4 cycles + RT (30-40 Gy to involved region) → Relapse, See Additional Therapy (TCEL-4)

Stage III, IV → Multiagent chemotherapy[h] x 6 cycles

• **PTCL, NOS**
• **ALCL, ALK -**
• **AITL** [g]
• **EATL**

→ **Stage I-IV** → Clinical trial (preferred) **or** Multiagent chemotherapy[h] 6 cycles ± RT (30-40 Gy for locoregional disease) → At completion of treatment, repeat all positive studies. If PET-CT scan positive, rebiopsy before changing course of treatment.

→ **Complete response**[j] → Clinical trial **or** Consider high-dose therapy with stem cell rescue[k] **or** Observe → Relapse, See Additional Therapy (TCEL-4)

→ **Partial response or no response or progressive disease**[j] → Relapse, See Additional Therapy (TCEL-4)

Breast implant-associated ALCL →
• Emerging entity described as development of ALCL around the implant (involving the fibrous capsule and/or seroma only). In this setting, the natural history of this entity appears generally favorable with surgical removal of the implant alone as adequate therapy for most patients.
• However, rare cases with parenchymal breast or nodal involvement may have an aggressive course more in line with systemic ALCL ALK.
• Optimal treatment of these cases is not well defined and management should be individualized.

[g] For selected patients (elderly, comorbid conditions), a trial of single-agent corticosteroid may be considered for symptom management.
[h] See Suggested Treatment Regimens (TCEL-B).

[j] See Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[k] Localized areas can be irradiated before or after high-dose therapy.

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| RELAPSE/ REFRACTORY DISEASE | ADDITIONAL THERAPY | | CONSOLIDATION/ ADDITIONAL THERAPY | RELAPSE #2 OR GREATER |

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

Relapse/ refractory disease

Candidate for transplant →

Clinical trial (preferred)
or
Second-line therapy
See Suggested Regimens (TCEL-B)

→ **Complete response[j]**
or
Partial response[j]

→ Clinical trial
or
Consider allogeneic stem cell transplant[k] (non-myeloablative or ablative)
or
Consider high-dose therapy with autologous stem cell rescue[k]

→ **Clinical trial**

No response →

Clinical trial
or
Best supportive care
or
Palliative RT

Non-candidate for transplant →

Clinical trial
or
Second-line therapy
See Suggested Regimens (TCEL-B)
or
Palliative RT

[j]See Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[k]Localized areas can be irradiated before or after high-dose therapy.

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INTERNATIONAL PROGNOSTIC INDEX[a]

ALL PATIENTS:
- Age >60 years
- Serum LDH > normal
- Performance status 2-4
- Stage III or IV
- Extranodal involvement >1 site

INTERNATIONAL INDEX, ALL PATIENTS:

• Low	0 or 1
• Low intermediate	2
• High intermediate	3
• High	4 or 5

AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX[a]

PATIENTS ≤60 YEARS:
- Stage III or IV
- Serum LDH > normal
- Performance status 2-4

INTERNATIONAL INDEX, PATIENTS ≤60 YEARS:

• Low	0
• Low/intermediate	1
• High/intermediate	2
• High	3

PROGNOSTIC INDEX FOR PTCL-U (PIT)[b]

RISK FACTORS:
- Age >60 years
- Serum LDH > normal
- Performance status 2-4
- Bone marrow involvement

PROGNOSTIC RISK:

• Group 1	0
• Group 2	1
• Group 3	2
• Group 4	3 or 4

[a] The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-hodgkin's lymphoma. N Engl J Med 1993;329:987-994.
[b] Gallamini A, Stelitano C, Calvi R, et al. Peripheral T-cell lymphoma unspecified (PTCL-U): A new prognostic model from a retrospective multicentric clinical study. Blood 2004;103:2474-2479.
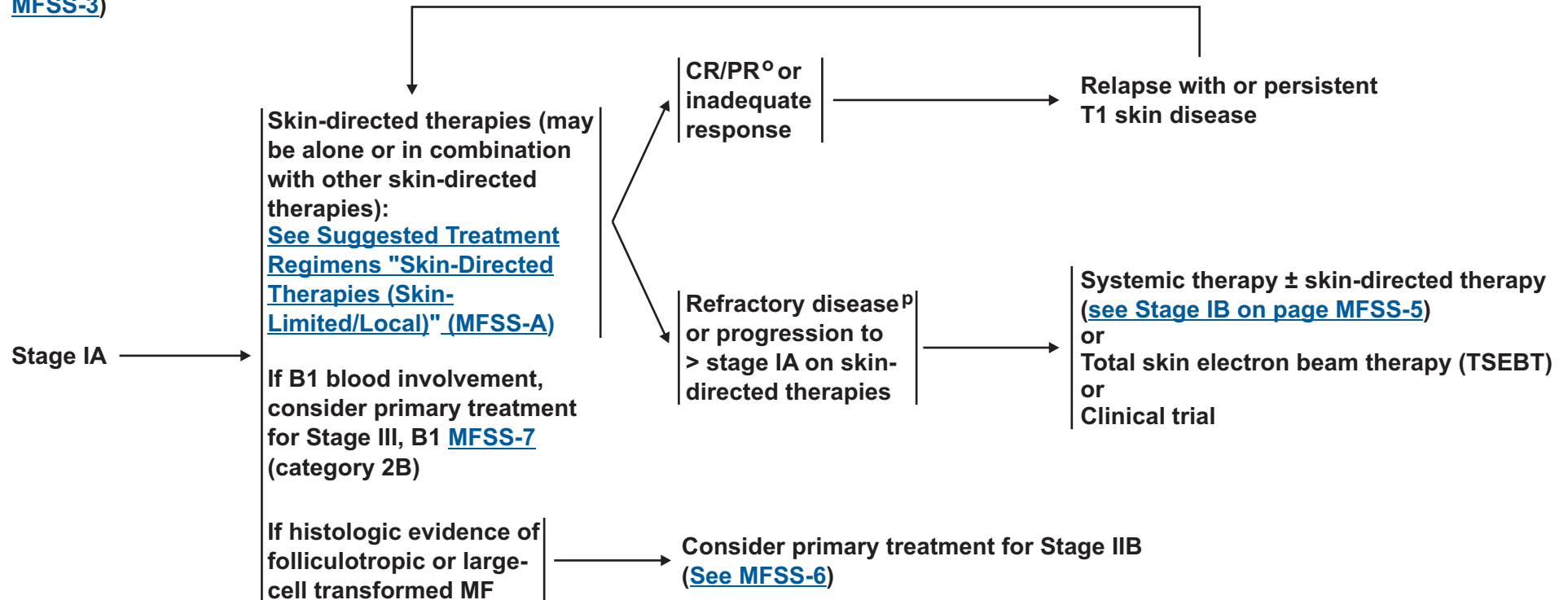
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SUGGESTED TREATMENT REGIMENS[a]
(in alphabetical order)

First-line Therapy:
- **Clinical trial[b]**
- **ALCL, ALK+ histology**
  - CHOP-21 (cyclophosphamide, doxorubicin, vincristine, prednisone)
  - CHOEP-21 (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone)
- **Other histologies (ALCL, ALK-; PTCL, NOS; AITL; EATL), regimens that can be used include:**
  - CHOEP
  - CHOP-14
  - CHOP-21
  - CHOP followed by ICE (ifosfamide, carboplatin, etoposide)
  - CHOP followed by IVE (ifosfamide, etoposide, epirubicin) alternating with intermediate-dose methotrexate [Newcastle Regimen] [studied only in patients with EATL]
  - Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
  - HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with high-dose methotrexate and cytarabine

First-line Consolidation:
- **Consider consolidation with high-dose therapy and stem cell rescue.**
  (ALCL, ALK + is a subtype with good prognosis and does not need consolidative transplant if in remission.)

Second-line Therapy (candidate for transplant):
- **Clinical trial preferred**
- **Belinostat (category 2B)**
- **Brentuximab vedotin for systemic ALCL excluding primary cutaneous ALCL**
- **Brentuximab vedotin for systemic CD30+ PTCL (category 2B)**
- **DHAP (dexamethasone, cisplatin, cytarabine)**
- **ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)**
- **Dose-adjusted EPOCH**
- **GDP (gemcitabine, dexamethasone, cisplatin)**
- **GemOx (gemcitabine, oxaliplatin)**
- **ICE (ifosfamide, carboplatin, etoposide)**
- **MINE (mesna, ifosfamide, mitoxantrone, etoposide)**
- **Pralatrexate[c]**
- **Romidepsin**

Second-line Therapy (non-candidate for transplant):
- **Clinical trial preferred**
- **Alemtuzumab[d]**
- **Belinostat (category 2B)**
- **Bortezomib[d]**
- **Brentuximab vedotin for systemic ALCL excluding primary cutaneous ALCL**
- **Brentuximab vedotin for systemic CD30+ PTCL (category 2B)**
- **Cyclosporine for AITL only[e]**
- **Dose-adjusted EPOCH**
- **Gemcitabine**
- **Pralatrexate[c]**
- **Radiation therapy**
- **Romidepsin**

[a]See references for regimens TCEL-B 2 of 2.
[b]While CHOP-21 and CHOEP-21 regimens confer a favorable prognosis in ALCL, ALK +, these regimens have not provided the same favorable results for other PTCL histologies; clinical trial is therefore preferred for the management of these other histologies.

[c]In AITL, pralatrexate has limited activity.
[d]Activity has been demonstrated in small clinical trials and additional larger trials are needed.
[e]With close follow-up of renal function.

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SUGGESTED TREATMENT REGIMENS
References

First-line Therapy
CHOP
Savage KJ, Chhanabhai M, Gascoyne RD, Connors JM. Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification. Ann Oncol 2004;15:1467-1475.
CHOP or CHOP-14 with or without etoposide
Pfreundschuh M, Trümper L, Kloess M, Schmits R, et al. German High-Grade Non-Hodgkin's Lymphoma Study Group. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: results of the NHL-B1 trial of the DSHNHL. Blood 2004;104:626-33.
Pfreundschuh M, Trümper L, Kloess M, Schmits R, et al. German High-Grade Non-Hodgkin's Lymphoma Study Group. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: Results of the NHL-B2 trial of the DSHNHL. Blood 2004;104:634-41.
Schmitz N, Trumper L, Ziepert M, et al. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood 2010;116:3418-3425.
CHOP followed by ICE
Horwitz S, Moskowitz C, Kewalramani T, et al. Second-line therapy with ICE followed by high dose therapy and autologous stem cell transplantation for relapsed/refractory peripheral T-cell lymphomas: Minimal benefit when analyzed by intent to treat [abstract]. Blood 2005;106:Abstract 2679.
CHOP followed by IVE
Sieniawski M, Lennard J, Millar C, et al. Aggressive primary chemotherapy plus autologous stem cell transplantation improves outcome for peripheral T cell lymphomas compared with CHOP-like regimens [abstract]. Blood 2009;114:Abstract1660.
Dose-adjusted EPOCH
Dunleavy K, Shovlin M, Pittaluga S, et al. DA-EPOCH Chemotherapy is highly effective in ALK-positive and ALK-negative ALCL: Results of a prospective study of PTCL subtypes in adults [abstract]. Blood 2011;118:Abstract 1618.
Wilson WH, Bryant G, Bates S, et al. EPOCH chemotherapy: toxicity and efficacy in relapsed and refractory non-Hodgkin's lymphoma. J Clin Oncol 1993;11:1573-582.
Peng YL, Huang HQ, Lin XB, et al. [Clinical outcomes of patients with peripheral T-cell lymphoma (PTCL) treated by EPOCH regimen]. Ai Zheng 2004;23:943-946.
HyperCVAD alternating with high-dose methotrexate and cytarabine
Escalon MP, Liu NS, Yang Y, et al. Prognostic factors and treatment of patients with T-cell non-Hodgkin lymphoma: the M. D. Anderson Cancer Center experience. Cancer 2005;103:2091-2098.
Pozadzides JV, Perini G, Hess M, et al. Prognosis and treatment of patients with peripheral T-cell lymphoma: The M. D. Anderson Cancer Center experience [abstract]. J Clin Oncol 2010;28: Abstract 8051.

Second-line Therapy
Alemtuzumab
Enblad G, Hagberg H, Erlanson M, et al. A pilot study of alemtuzumab (anti-CD52 monoclonal antibody) therapy for patients with relapsed or chemotherapy-refractory peripheral T-cell lymphomas. Blood 2004;103:2920-2924.
Bel

Belinostat
O'Connor O, Masszi T, Savage K, et al. Belinostat, a novel pan-histone deacetylase inhibitor (HDACi), in relapsed or refractory peripheral T-cell lymphoma (R/R PTCL): Results from the BELIEF trial [abstract]. J Clin Oncol 2013;31:Abstact 8507.
Brentuximab vedotin
Pro B, Advani R, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: Results of a phase II study. J Clin Oncol 2012;30:2190-2196.
Jacobsen ED, Advani RH, Oki Y, et al. A Phase 2 Study of Brentuximab Vedotin in Patients with Relapsed or Refractory CD30-Positive Non-Hodgkin Lymphomas: Interim Results [abstract]. Blood 2012;120: Abstract 2746.
Cyclosporine for AITL
Advani R, Horwitz S, Zelenetz A, Horning SJ. Angioimmunoblastic T cell lymphoma: treatment experience with cyclosporine. Leuk Lymphoma 2007;48:521-525.
DHAP (dexamethasone, cisplatin, cytarabine)
Velasquez WS, Cabanillas F, Salvador P, et al. Effective salvage therapy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone (DHAP). Blood 1988;71:117-122.
Mey UJ, Orlopp KS, Flieger D, et al. Dexamethasone, high-dose cytarabine, and cisplatin in combination with rituximab as salvage treatment for patients with relapsed or refractory aggressive non-Hodgkin's lymphoma. Cancer Invest 2006;24:593-600.
ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)
Velasquez WS, McLaughlin P, Tucker S, et al. ESHAP - an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. J Clin Oncol 1994;12:1169-1176.
Gemcitabine
Zinzani PL, Baliva G, Magagnoli M, et al. Gemcitabine treatment in pretreated cutaneous T-cell lymphoma: Experience in 44 patients. J Clin Oncol 2000;18:2603-2606.
Zinzani PL, Magagnoli M, Bendandi M, et al. Therapy with gemcitabine in pretreated peripheral T-cell lymphoma patients. Ann Oncol 1998;9:1351-1353.
GDP (gemcitabine, dexamethasone, cisplatin)
Crump M, Baetz T, Couban S, et al. Gemcitabine, dexamethasone, and cisplatin in patients with recurrent or refractory aggressive histology B-cell non-Hodgkin lymphoma: a Phase II study by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG). Cancer 2004;101:1835-1842.
Dong M, He XH, Liu P, et al. Gemcitabine-based combination regimen in patients with peripheral T-cell lymphoma. Med Oncol 2013;30:351.
GemOX (gemcitabine, oxaliplatin)
Lopez A, Gutierrez A, Palacios A, et al. GEMOX-R regimen is a highly effective salvage regimen in patients with refractory/relapsing diffuse large-cell lymphoma: A phase II study. Eur J Haematol 2008;80:127-132.
ICE (ifosfamide, carboplatin, etoposide)
Zelenetz AD, Hamlin P, Kewalramani T, et al. Ifosfamide, carboplatin, etoposide (ICE)-based second-line chemotherapy for the management of relapsed and refractory aggressive non-Hodgkin's lymphoma. Ann Oncol 2003;14[suppl 1]:i5-10.
Pralatrexate
O'Connor OA, Pro B, Pinter-Brown L, et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: Results from the pivotal PROPEL study. J Clin Oncol 2011;29:1182-1189.
Romidepsin
Coiffier B, Pro B, Prince HM, et al. Results From a Pivotal, Open-Label, Phase II Study of Romidepsin in Relapsed or Refractory Peripheral T-Cell Lymphoma After Prior Systemic Therapy. J Clin Oncol 2012;30:631-636.

Note: All recommendations are category 2A unless otherwise indicated.
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TCEL-B

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Mycosis Fungoides/Sezary Syndrome

DIAGNOSIS

ESSENTIAL:
- Biopsy of suspicious skin sites
- Dermatopathology review of slides

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- IHC panel of skin biopsy[a,b,c]
  - CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, CD25, CD56, TIA1, granzyme B, βF1, TCR-CγM1
- Molecular analysis of skin biopsy: TCR gene rearrangements (assessment of clonality)[a] by PCR methods[d]
- Assessment of peripheral blood for Sezary cells (in cases where skin is not diagnostic, especially T4) including:
  - Sezary cell prep
  - Flow cytometry (CD3, CD4, CD7, CD8, CD26 to assess for expanded CD4+ cells with increased CD4/CD8 ratio or with abnormal immunophenotype, including loss of CD7 or CD26) and
  - PCR for TCR gene rearrangement
- Biopsy of suspicious lymph nodes (in absence of definitive skin diagnosis)
- Assessment of HTLV-1[e] serology in at-risk populations. HTLV-1 PCR if serology is indeterminate

WORKUP

ESSENTIAL:
- Complete physical examination:
  - Examination of entire skin: assessment of %BSA (palm plus digits ≈1% BSA) and type of skin lesion (patch/plaque, tumor, erythroderma)
  - Palpation of peripheral lymph node regions
  - Palpation for organomegaly/masses
- Laboratory studies:[f]
  - CBC with Sezary screen (manual slide review, "Sezary cell prep")
  - Sezary flow cytometric study (optional for T1);
  - TCR gene rearrangement of peripheral blood lymphocytes if blood involvement suspected
  - Comprehensive metabolic panel
  - LDH
- Imaging studies:
  - Chest/abdominal/pelvic contrast-enhanced CT or integrated whole body PET-CT (≥T2, large cell transformed or folliculotropic MF, or with palpable adenopathy or abnormal laboratory studies)
- Pregnancy testing in women of child-bearing age[g]

USEFUL IN SELECTED CASES:
- Bone marrow biopsy (not required for staging but used to document visceral disease in those suspected to have marrow involvement including B2 blood involvement and in patients with unexplained hematologic abnormality)
- Biopsy of suspicious lymph nodes for identical clones (recommend assessment of clonality for all but particularly NCI LN 2-3) or suspected extracutaneous sites
- Rebiopsy if suspicious of large cell transformation
- Neck CT

STAGE
(MFSS-2 and MFSS-3)

Stage IA → See Primary Treatment (MFSS-4)

Stage IB-IIA → See Primary Treatment (MFSS-5)

Stage IIB → See Primary Treatment (MFSS-6)

Stage III → See Primary Treatment (MFSS-7)

Stage IV → See Primary Treatment (MFSS-8)

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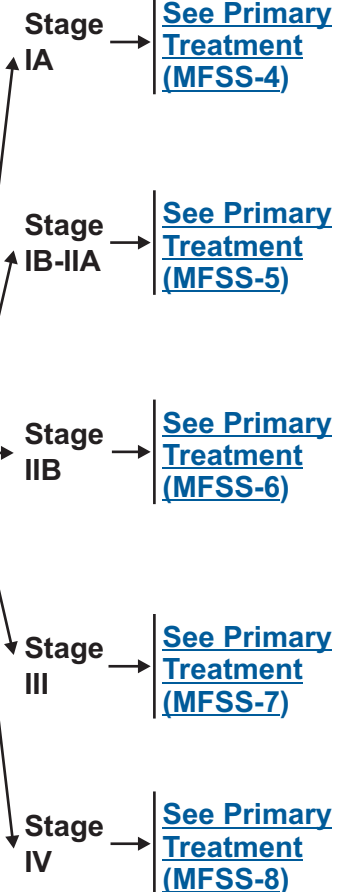
[a] Clinically or histologically non-diagnostic cases. Pimpinelli N, Olsen EA, Santucci M, et al, for the International Society for Cutaneous Lymphoma. Defining early mycosis fungoides. J Am Acad Dermatol 2005;53:1053-1063.

[b] See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).

[c] Typical immunophenotype: CD2+ CD3+ CD5+ CD7- CD4+ CD8- (rarely CD8+) CD30-/+ cytotoxic granule proteins negative.

[d] TCR gene rearrangement results should be interpreted with caution. TCR clonal rearrangement can be seen in non-malignant conditions or may not be demonstrated in all cases of MF/SS. Demonstration of identical clones in skin, blood, and/or lymph node may be helpful in selected cases.

[e] See map for prevalence of HTLV-1 by geographic region.

[f] Sezary syndrome (B2) is as defined on MFSS-2.

[g] Many skin-directed and systemic therapies are contraindicated or of unknown safety in pregnancy. Refer to individual drug information.

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TNMB		TNMB Classification and Staging of Mycosis Fungoides and Sezary Syndrome[h,i]
Skin	T1	Limited patches,[j] papules, and/or plaques[k] covering <10% of the skin surface
	T2	Patches,[j] papules, and/or plaques[k] covering ≥10% of the skin surface
	T3	One or more tumors[l] (≥1 cm in diameter)
	T4	Confluence of erythema ≥80% body surface area
Node	N0	No abnormal lymph nodes; biopsy not required
	N1	Abnormal lymph nodes; histopathology Dutch Gr 1 or NCI LN 0-2
	N2	Abnormal lymph nodes; histopathology Dutch Gr 2 or NCI LN 3
	N3	Abnormal lymph nodes; histopathology Dutch Gr 3-4 or NCI LN 4
	NX	Abnormal lymph nodes; no histologic confirmation
Visceral	M0	No visceral organ involvement
	M1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
	MX	Abnormal visceral site; no histologic confirmation
Blood	B0	Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes are atypical (Sezary) cells
	B1	Low blood tumor burden: >5% of peripheral blood lymphocytes are atypical (Sezary) cells but do not meet the criteria of B2
	B2	High blood tumor burden: ≥1000/mcL Sezary cells[i] or CD4/CD8 ≥10 or ≥40% CD4+/CD7- or ≥30% CD4+/CD26- cells

[j] Patch = Any size skin lesion without significant elevation or induration. Presence/absence of hypo- or hyperpigmentation, scale, crusting, and/or poikiloderma should be noted.

[k] Plaque = Any size skin lesion that is elevated or indurated. Presence or absence of scale, crusting and/or poikiloderma should be noted. Histologic features such as folliculotropism or large cell transformation (≥25% large cells), CD30+ or CD30-, and clinical features such as ulceration are important to document.

[h] Adapted from Olsen E, Vonderheid E, Pimpinelli N, et al. Blood 2007;110:1713-1722.

[i] Sezary syndrome (B2) is defined as a clonal rearrangement of the TCR in the blood (clones should be relevant to clone in the skin) and either ≥1000/mcL or increased CD4 or CD3 cells with CD4/CD8 of ≥10 or increase in CD4 cells with an abnormal phenotype (≥40% CD4+/CD7- or ≥30% CD4+/CD26- of the total lymphocyte count).

[l] Tumor = at least one >1 cm diameter solid or nodular lesion with evidence of depth and/or vertical growth. Note total number of lesions, total volume of lesions, largest size lesion, and region of body involved. Also note if histologic evidence of large cell transformation has occurred. Phenotyping for CD30 is encouraged.

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Clinical Staging of MF and SS[h]

	T	N	M	B
IA IB	1 2	0 0	0 0	0,1 0,1
IIA IIB	1-2 3	1,2 0-2	0 0	0,1 0,1
IIIA IIIB	4 4	0-2 0-2	0 0	0 1
IVA_1 IVA_2 IVB	1-4 1-4 1-4	0-2 3 0-3	0 0 1	2 0-2 0-2

[h] Olsen E, Vonderheid E, Pimpinelli N, et al. Blood 2007;110:1713-1722.

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STAGE (MFSS-2 and MFSS-3)

PRIMARY TREATMENT[m]

RESPONSE TO THERAPY[n]

See Supportive Care for MF/SS (MFSS-B)

Stage IA →

Skin-directed therapies (may be alone or in combination with other skin-directed therapies):
See Suggested Treatment Regimens "Skin-Directed Therapies (Skin-Limited/Local)" (MFSS-A)

If B1 blood involvement, consider primary treatment for Stage III, B1 MFSS-7 (category 2B)

If histologic evidence of folliculotropic or large-cell transformed MF

CR/PR[o] or inadequate response → **Relapse with or persistent T1 skin disease**

Refractory disease[p] or progression to > stage IA on skin-directed therapies → **Systemic therapy ± skin-directed therapy (see Stage IB on page MFSS-5) or Total skin electron beam therapy (TSEBT) or Clinical trial**

→ **Consider primary treatment for Stage IIB (See MFSS-6)**

[m] It is preferred that treatment occur at centers with expertise in the management of the disease.

[n] Unlike other NHL subtypes, response criteria for MF/SS has not been demonstrated to correlate with prognosis. Often decisions to continue or switch therapy are on a clinical basis. However, a proposal for detailed response criteria has been published (Olsen E, Whittaker S, Kim YH, et al. J Clin Oncol 2011;29:2598-2607).

[o] Patients achieving a response and/or a clinical benefit should be considered for maintenance or taper regimens to optimize response duration. Patients who relapse often respond well to the same treatment. Patients with a PR should be treated with the other options in the primary treatment list to improve response before moving onto treatment for refractory disease. Patients with relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

[p] Refractory or intolerant to multiple previous therapies.

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See Supportive Care for MF/SS (MFSS-B)

STAGE
(MFSS-2 and MFSS-3)

PRIMARY TREATMENT[m]

RESPONSE TO THERAPY[n]

Stage IB-IIA →

Generalized skin treatment
• See Suggested Treatment Regimens "Skin-Directed Therapies (Skin-Generalized)" (MFSS-A) ± adjuvant local skin treatment[q] (see stage IA on MFSS-4)

If blood B1 involvement, consider primary treatment for Stage III B1 MFSS-7 (category 2B)

If histologic evidence of folliculotropic or large-cell transformed MF → **Consider primary treatment for Stage IIB (See MFSS-6)**

CR/PR[o] or inadequate response →

Refractory disease[p] or progression to > stage IB-IIA →

Relapse with or persistent T1-T2 disease:
• T1 (see stage IA on MFSS-4)
• T2 (see generalized skin treatment) (MFSS-A)

See Suggested Treatment Regimens
• Clinical trial
• Systemic Therapies (SYST-CAT A) (MFSS-A)
• Combination Therapies ± skin-directed therapy

CR/PR[o] or inadequate response

Refractory disease[p] or progression →

• Clinical trial
• TSEBT (if not previously administered)
• Systemic chemotherapy agents used in ≥ stage IIB disease
  ‣ See Suggested Treatment Regimens "Systemic Therapies (SYST-CAT B)" (MFSS-A)

[m] It is preferred that treatment occur at centers with expertise in the management of the disease.

[n] Unlike other NHL subtypes, response criteria for MF/SS has not been demonstrated to correlate with prognosis. Often decisions to continue or switch therapy are on a clinical basis. However, a proposal for detailed response criteria has been published (Olsen E, Whittaker S, Kim YH, et al. J Clin Oncol 2011;29:2598-2607).

[o] Patients achieving a response and/or a clinical benefit should be considered for maintenance or taper regimens to optimize response duration. Patients who relapse often respond well to the same treatment. Patients with a PR should be treated with the other options in the primary treatment list to improve response before moving onto treatment for refractory disease. Patients with relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

[p] Refractory or intolerant to multiple previous therapies.

[q] For patients with recalcitrant sites after generalized skin treatment, additional local treatment may be needed.

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STAGE
(MFSS-2 and MFSS-3)

PRIMARY TREATMENT[m]

RESPONSE TO THERAPY[n]

Stage IIB[r] and/or histologic evidence of folliculotropic or large-cell transformation (LCT)

Limited extent tumor disease ± patch/plaque disease

→

- **Local RT for limited extent tumor, transformed, and/or folliculotropic disease[u]**
- **Systemic Therapies (SYST-CAT A) (MFSS-A) ± skin-directed therapies[v] ± RT**

→

CR/PR[o] or inadequate response →

Relapse with or persistent T1-T3 limited:
- T1-2 (see stage IA on MFSS-4 or stage IB-IIA on MFSS-5)
- T3 limited extent

Refractory disease[p] or progression

Generalized extent tumor, transformed, and/or folliculotropic disease[s,t]

→

- **TSEBT[w]**
- **See Suggested Treatment Regimens[s,t]**
  - ▸ Systemic Therapies (SYST-CAT A) (MFSS-A)
  - ▸ Systemic Therapies (SYST-CAT B) (MFSS-A)
  - ▸ Systemic Therapies (SYST-CAT C) (MFSS-A)
  - ▸ Combination Therapies
- **± skin-directed therapy**

→

CR/PR[o] or inadequate response →

Relapse with or persistent T1-T3:
- T1-2 (see stage IA on MFSS-4 or stage IB-IIA on MFSS-5)
- T3

Refractory disease[p] or progression →

- **Multi-agent chemotherapy[x]**
- **Consider allogeneic transplant[y]**
- **Clinical trial**

See Supportive Care for MF/SS (MFSS-B)

[m] It is preferred that treatment occur at centers with expertise in the management of the disease.

[n] Unlike other NHL subtypes, response criteria for MF/SS has not been demonstrated to correlate with prognosis. Often decisions to continue or switch therapy are on a clinical basis. However, a proposal for detailed response criteria has been published (Olsen E, Whittaker S, Kim YH, et al. J Clin Oncol 2011;29:2598-2607).

[o] Patients achieving a response and/or a clinical benefit should be considered for maintenance or taper regimens to optimize response duration. Patients who relapse often respond well to the same treatment. Patients with a PR should be treated with the other options in the primary treatment list to improve response before moving onto treatment for refractory disease. Patients with relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

[p] Refractory or intolerant to multiple previous therapies.

[r] Rebiopsy if suspect large cell transformation.

[s] Histologic evidence of LCT often, but not always corresponds to a more aggressive growth rate. If there is no evidence of more aggressive growth, choosing systemic therapies from SYST-CAT A or SYST-CAT B are appropriate. If aggressive growth is seen, then agents listed in SYST-CAT C are preferred.

[t] Patients with indolent/plaque folliculotropic MF (without evidence of LCT) should first be considered for therapies under SYST-CAT A before resorting to treatments listed in SYST CAT B or SYST CAT C.

[u] For non-radiated sites, see Stage I-IIA. After patient is rendered disease free by RT, may consider adjuvant systemic biologic therapy (SYST-CAT A) after RT to improve response duration.

[v] Skin-directed therapies are for patch or plaque lesions and not for tumor lesions.

[w] May consider adjuvant systemic biologic therapy (SYST-CAT A) after TSEBT to improve response duration.

[x] Most patients are treated with multiple SYST-CAT A/B or combination therapies before receiving multiagent chemotherapy.

[y] The role of allogeneic HSCT is controversial. See Discussion for further details.

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STAGE (MFSS-2 and MFSS-3)　　**PRIMARY TREATMENT^m**　　**RESPONSE TO THERAPY^n**

See Supportive Care for MF/SS (MFSS-B)

See monoclonal antibody and viral reactivation (NHODG-B)

Stage III^z →

If no blood involvement, consider skin-directed therapy
See Suggested Treatment Regimens Skin-Directed Therapies (Skin-Generalized) (MFSS-A)
or
If blood B1 involvement, systemic therapies
See Suggested Treatment Regimens "Systemic Therapies (SYST-CAT A)" ± skin-directed therapy^{aa}

→ CR/PR^o or inadequate response → Relapse or persistent disease

→ Refractory disease^p or progression →

- Combination therapies
  ➤ See Suggested Treatment Regimens - Combination Therapies^{bb} (MFSS-A)
- Clinical trial

→ CR/PR^o or inadequate response → Relapse or persistent disease

→ Refractory disease^p or progression →

- Clinical trial
- See Suggested Treatment Regimens Systemic Therapies (SYST-CAT B)
- Alemtuzumab^{cc}
- Consider nonablative allogeneic transplant,^{y} as appropriate

---

^{m} It is preferred that treatment occur at centers with expertise in the management of the disease.

^{n} Unlike other NHL subtypes, response criteria for MF/SS has not been demonstrated to correlate with prognosis. Often decisions to continue or switch therapy are on a clinical basis. However, a proposal for detailed response criteria has been published (Olsen E, Whittaker S, Kim YH, et al. J Clin Oncol 2011;29:2598-2607).

^{o} Patients achieving a response and/or a clinical benefit should be considered for maintenance or taper regimens to optimize response duration. Patients who relapse often respond well to the same treatment. Patients with a PR should be treated with the other options in the primary treatment list to improve response before moving onto treatment for refractory disease. Patients with relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

^{p} Refractory or intolerant to multiple previous therapies.

^{y} The role of allogeneic HSCT is controversial. See Discussion for further details.

^{z} Generalized skin-directed therapies (other than topical steroids) may not be well-tolerated in stage III and should be used with caution. Phototherapy (PUVA or UVB) or TSEBT can be used successfully.

^{aa} Mid-potency topical steroids should be included (± occlusive modality) with any of the primary treatment modalities to reduce skin symptoms. Erythrodermic patients are at increased risk for secondary infection with skin pathogens and systemic antibiotic therapy should be considered.

^{bb} Combination therapy options can be considered earlier (primary treatment) depending on treatment availability or symptom severity.

^{cc} Lower doses of alemtuzumab administered subcutaneously have shown lower incidence of infectious complications.

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STAGE (MFSS-2 and MFSS-3)

PRIMARY TREATMENT[m]

RESPONSE TO THERAPY[n]

Stage IV

Sezary syndrome →
- See Suggested Treatment Regimens
  - ▶ Systemic Therapies (SYST-CAT A) (MFSS-A)
  - ▶ Combination Therapies

→ CR/PR[o] or inadequate response → Relapse or persistent disease
- Consider allogeneic transplant,[y] as appropriate

→ Refractory disease[p] or progression →
- See Suggested Treatment Regimens - Systemic Therapies (SYST-CAT B) (MFSS-A)
- Alemtuzumab[cc]
- Clinical trial

Non Sezary or Visceral disease (solid organ) →
See Suggested Treatment Regimens - Systemic Therapies (SYST-CAT B) or (SYST-CAT C)[dd] or multi-agent chemotherapy ± RT for local control[ee]

→ CR/PR[o] or inadequate response → Relapse or persistent disease
- Consider allogeneic transplant,[y] as appropriate

→ Refractory disease[p] or progression → Clinical trial

See Supportive Care for MF/SS (MFSS-B)

See monoclonal antibody and viral reactivation (NHODG-B)

[m] It is preferred that treatment occur at centers with expertise in the management of the disease.

[n] Unlike other NHL subtypes, response criteria for MF/SS has not been demonstrated to correlate with prognosis. Often decisions to continue or switch therapy are on a clinical basis. However, a proposal for detailed response criteria has been published (Olsen E, Whittaker S, Kim YH, et al. J Clin Oncol 2011;29:2598-2607).

[o] Patients achieving a response and/or a clinical benefit should be considered for maintenance or taper regimens to optimize response duration. Patients who relapse often respond well to the same treatment. Patients with a PR should be treated with the other options in the primary treatment list to improve response before moving onto treatment for refractory disease. Patients with relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

[p] Refractory or intolerant to multiple previous therapies.

[y] The role of allogeneic HSCT is controversial. See Discussion for further details.

[cc] Lower doses of alemtuzumab administered subcutaneously have shown lower incidence of infectious complications.

[dd] Patients with stage IV non-Sezary/visceral disease may present with more aggressive growth characteristics. If there is no evidence of more aggressive growth, systemic therapies from SYST-CAT B are appropriate. If aggressive growth is seen, then agents listed in SYST-CAT C are preferred.

[ee] Consider adjuvant systemic biologic therapy (SYST-CAT A) after chemotherapy to improve response duration.

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SUGGESTED TREATMENT REGIMENS[a]

SKIN-DIRECTED THERAPIES

For limited/localized skin involvement (Skin-Limited/Local)
- Topical corticosteroids[b]
- Topical chemotherapy (mechlorethamine [nitrogen mustard], carmustine)
- Local radiation (8-36 Gy)
- Topical retinoids (bexarotene, tazarotene)
- Phototherapy (UVB, nbUVB for patch/thin plaques; PUVA for thicker plaques)[c]
- Topical imiquimod

For generalized skin involvement (Skin-Generalized)
- Topical corticosteroids[b]
- Topical chemotherapy (mechlorethamine [nitrogen mustard], carmustine)
- Phototherapy (UVB, nbUVB, for patch/thin plaques; PUVA for thicker plaques)[c]
- Total skin electron beam therapy (TSEBT) (12-36 Gy)[d] (reserved for those with severe skin symptoms or generalized thick plaque or tumor disease, or poor response to other therapies)

SYSTEMIC THERAPIES

Category A (SYST-CAT A)
- Retinoids (bexarotene, all-trans retinoic acid, isotretinoin [13-cis-retinoic acid], acitretin)
- Interferons (IFN-alpha, IFN-gamma)
- HDAC-inhibitors (vorinostat, romidepsin)[e]
- Extracorporeal photopheresis[f]
- Methotrexate (≤100 mg q week)

Category B (SYST-CAT B)
- First-line therapies
  - ➤ Liposomal doxorubicin
  - ➤ Gemcitabine
- Second-line therapies
  - ➤ Chlorambucil
  - ➤ Pentostatin
  - ➤ Etoposide
  - ➤ Cyclophosphamide
  - ➤ Temozolomide
  - ➤ Methotrexate (>100 mg q week)
  - ➤ Low-dose pralatrexate

SYSTEMIC THERAPIES (continued)

Category C (SYST-CAT C)[g]
- Liposomal doxorubicin
- Gemcitabine
- Romidepsin
- Low- or standard-dose pralatrexate
- See regimens listed on TCEL-B[h]

COMBINATION THERAPIES

Skin-directed + Systemic
- Phototherapy + retinoid[e]
- Phototherapy + IFN
- Phototherapy + photopheresis[f]
- Total skin electron beam + photopheresis[f]

Systemic + Systemic
- Retinoid + IFN
- Photopheresis[f] + retinoid
- Photopheresis[f] + IFN
- Photopheresis[f] + retinoid + IFN

[a] See references for regimens MFSS-A 2 of 4, MFSS-A 3 of 4, and MFSS-A 4 of 4.

[b] Long-term use of topical steroid may be associated with skin atrophy and/or striae formation. This risk worsens with increased potency of the steroid. High-potency steroid used on large skin surfaces may lead to systemic absorption.

[c] Cumulative dose of UV is associated with increased risk of UV-associated skin neoplasms; thus, phototherapy may not be appropriate in patients with a history of extensive squamoproliferative skin neoplasms or basal cell carcinomas or who have had melanoma.

[d] It is common practice to follow TSEBT with systemic therapies such as interferon or bexarotene to maintain response.

[e] Safety of combining TSEBT with systemic retinoids or HDAC inhibitors, such as vorinostat or romidepsin, or combining phototherapy with vorinostat or romidepsin is unknown.

[f] Photopheresis may be more appropriate as systemic therapy in patients with some blood involvement (B1 or B2).

[g] Patients with large cell transformed (LCT) MF and stage IV non-Sezary/visceral disease may present with more aggressive growth characteristics. In general, agents listed in SYST-CAT C are preferred in these circumstances.

[h] Combination regimens are generally reserved for patients with relapsed/refractory or extracutaneous disease.

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References

Skin-directed Therapies
Topical corticosteroids
Zackheim HS, Kashani Sabet M, Amin S. Topical corticosteroids for mycosis fungoides. Experience in 79 patients. Arch Dermatol 1998;134(8):949-954.
Zackheim HS. Treatment of patch stage mycosis fungoides with topical corticosteroids. Dermatol Ther 2003;16:283-287.

Carmustine
Zackheim HS. Topical carmustine (carmustine) in the treatment of mycosis fungoides. Dermatol Ther 2003;16:299-302.

Nitrogen mustard (mechlorethamine hydrochloride)
Kim YH, Martinez G, Varghese A, Hoppe RT. Topical nitrogen mustard in the management of mycosis fungoides: Update of the Stanford experience. Arch Dermatol 2003;139:165-173.
Lessin SR, Duvic M, Guitart J, et al. Topical chemotherapy in cutaneous T-cell lymphoma: positive results of a randomized, controlled, multicenter trial testing the efficacy and safety of a novel mechlorethamine, 0.02%, gel in mycosis fungoides. JAMA Dermatol 2013;149:25-32.

Local radiation
Wilson LD, Kacinski BM, Jones GW. Local superficial radiotherapy in the management of minimal stage IA cutaneous T-cell lymphoma (Mycosis Fungoides). Int J Radiat Oncol Biol Phys 1998;40:109-115.
Neelis KJ, Schimmel EC, Vermeer MH, et al. Low-dose palliative radiotherapy for cutaneous B- and T-cell lymphomas. Int J Radiat Oncol Biol Phys 2009;74:154-158.
Thomas TO, Agrawal P, Guitart J, et al. Outcome of patients treated with a single-fraction dose of palliative radiation for cutaneous T-cell lymphoma. Int J Radiat Oncol Biol Phys 2013;85:747-753

Topical bexarotene
Breneman D, Duvic M, Kuzel T, et al. Phase 1 and 2 trial of bexarotene gel for skin directed treatment of patients with cutaneous T cell lymphoma. Arch Dermatol 2002;138:325-332.
Heald P, Mehlmauer M, Martin AG, et al. Topical bexarotene therapy for patients with refractory or persistent early stage cutaneous T cell lymphoma: results of the phase III clinical trial. J Am Acad Dermatol 2003;49:801-815.

Tazarotene Gel
Apisarnthanarax N, Talpur R, Ward S, Ni X, Kim HW, Duvic M. Tazarotene 0.1% gel for refractory mycosis fungoides lesions: an open-label pilot study. J Am Acad Dermatol 2004;50:600-607.

Topical imiquimod
Deeths MJ, Chapman JT, Dellavalle RP, Zeng C, Aeling JL. Treatment of patch and plaque stage mycosis fungoides with imiquimod 5% cream. J Am Acad Dermatol 2005;52:275-280.

Photography (UVB and PUVA)

Gathers RC, Scherschun L, Malick F, Fivenson DP, Lim HW. Narrowband UVB phototherapy for early stage mycosis fungoides. J Am Acad Dermatol 2002;47:191-197.
Querfeld C, Rosen ST, Kuzel TM, et al. Long term follow up of patients with early stage cutaneous T cell lymphoma who achieved complete remission with psoralen plus UVA monotherapy. Arch Dermatol 2005;141:305-311.
Ponte P, Serrao V, Apetato M. Efficacy of narrowband UVB vs. PUVA in patients with early-stage mycosis fungoides. J Eur Acad Dermatol Venereol 2010;24:716-721.

Total skin electron beam therapy (TSEBT)
Chinn DM, Chow S, Kim YH, Hoppe RT. Total skin electron beam therapy with or without adjuvant topical nitrogen mustard or nitrogen mustard alone as initial treatment of T2 and T3 mycosis fungoides. Int J Radiat Oncol Biol Phys 1999;43:951-958.
Ysebaert L, Truc G, Dalac S et al. Ultimate results of radiation therapy for T1-T2 mycosis fungoides. Int J Radiat Oncol Biol Phys 2004;58:1128-1134.
Harrison C, Young J, Navi D, et al. Revisiting low-dose total skin electron beam therapy in mycosis fungoides. Int J Radiat Oncol Biol Phys 2011;81:e651-657.

Systemic Therapies
Alemtuzumab for Sezary syndrome ± lymph node disease
Lundin J, Hagberg H, Repp R, et al. Phase 2 study of alemtuzumab (anti-CD52 monoclonal antibody) in patients with advanced mycosis fungoides/Sezary syndrome. Blood 2003;101:4267-4272.
Bernengo MG, Quaglino P, Comessatti A, et al. Low-dose intermittent alemtuzumab in the treatment of Sezary syndrome: clinical and immunologic findings in 14 patients. Haematologica 2007;92:784-794.
Gautschi O, Blumenthal N, Streit M, et al. Successful treatment of chemotherapy-refractory Sezary syndrome with alemtuzumab (Campath-1H). Eur J Haematol 2004;72:61-63.
Querfeld C, Mehta N, Rosen ST, et al. Alemtuzumab for relapsed and refractory erythrodermic cutaneous T-cell lymphoma: a single institution experience from the Robert H. Lurie Comprehensive Cancer Center. Leuk Lymphoma 2009;50:1969-1976.

Retinoids
Zhang C, Duvic M. Treatment of cutaneous T-cell lymphoma with retinoids. Dermatol Ther 2006;19:264-271.
Duvic M, Martin AG, Kim Y, et al. Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. Arch Dermatol 2001;137:581-593.
Duvic M, Hymes K, Heald P, et al. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. J Clin Oncol 2001;19:2456-2471.

Interferon
Olsen EA. Interferon in the treatment of cutaneous T-cell lymphoma. Dermatol Ther 2003;16:311-321.
Kaplan EH, Rosen ST, Norris DB, et al. Phase II study of recombinant human interferon gamma for treatment of cutaneous T-cell lymphoma. J Natl Cancer Inst 1990;82:208-212.

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Systemic Therapies Continued

Vorinostat

Duvic M, Talpur R, Ni X, et al. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). Blood 2007;109:31-39.

Olsen EA, Kim YH, Kuzel TM, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. J Clin Oncol 2007;25:3109-3115.

Duvic M, Olsen EA, Breneman D, et al. Evaluation of the long-term tolerability and clinical benefit of vorinostat in patients with advanced cutaneous T-cell lymphoma. Clin Lymphoma Myeloma 2009;9:412-416.

Romidepsin

Piekarz RL, Frye R, Turner M, et al. Phase II Multi-Institutional Trial of the Histone Deacetylase Inhibitor Romidepsin As Monotherapy for Patients With Cutaneous T-Cell Lymphoma. J Clin Oncol 2009;27:5410-5417.

Whittaker SJ, Demierre MF, Kim EJ, et al. Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. J Clin Oncol 2010; 28:4485-4491.

Extracorporeal photopheresis (ECP)

Edelson R, Berger C, Gasparro F, et al. Treatment of cutaneous T-cell lymphoma by extracorporeal photochemotherapy. Preliminary results. N Engl J Med 1987;316:297-303.

Zic JA, Stricklin GP, Greer JP, et al. Long-term follow-up of patients with cutaneous T-cell lymphoma treated with extracorporeal photochemotherapy. J Am Acad Dermatol 1996;35:935-945.

Zic JA. The treatment of cutaneous T-cell lymphoma with photopheresis. Dermatol Ther 2003;16:337-346.

Methotrexate

Zackheim HS, Kashani-Sabet M, Hwang ST. Low-dose methotrexate to treat erythrodermic cutaneous T-cell lymphoma: results in twenty-nine patients. J Am Acad Dermatol 1996;34:626-631.

Zackheim HS, Kashani-Sabet M, McMillan A. Low-dose methotrexate to treat mycosis fungoides: a retrospective study in 69 patients. J Am Acad Dermatol 2003;49:873-878.

Liposomal doxorubicin

Wollina U, Dummer R, Brockmeyer NH, et al. Multicenter study of pegylated liposomal doxorubicin in patients with cutaneous T-cell lymphoma. Cancer 2003;98:993-1001.

Quereux G, Marques S, Nguyen J-M, et al. Prospective multicenter study of pegylated liposomal doxorubicin treatment in patients with advanced or refractory mycosis fungoides or Sezary syndrome. Arch Dermatol 2008;144:727-733.

Dummer R, Quaglino P, Becker JC, et al. Prospective international multicenter phase II trial of intravenous pegylated liposomal doxorubicin monochemotherapy in patients with stage IIB, IVA, or IVB advanced mycosis fungoides: final results from EORTC 21012. J Clin Oncol 2012;30:4091-4097.

Gemcitabine

Duvic M, Talpur R, Wen S, Kurzrock R, David CL, Apisarnthanarax N. Phase II evaluation of gemcitabine monotherapy for cutaneous T-cell lymphoma. Clin Lymphoma Myeloma 2006;7:51-58.

Marchi E, Alinari L, Tani M, et al. Gemcitabine as frontline treatment for cutaneous T-cell lymphoma: phase II study of 32 patients. Cancer 2005;104:2437-2441.

Zinzani PL, Baliva G, Magagnoli M, et al. Gemcitabine treatment in pretreated cutaneous T-cell lymphoma: experience in 44 patients. J Clin Oncol 2000;18:2603-2606.

Zinzani PL, Venturini F, Stefoni V, et al. Gemcitabine as single agent in pretreated T-cell lymphoma patients: evaluation of the long-term outcome. Ann Oncol 2010;21:860-863.

Awar O, Duvic M. Treatment of transformed mycosis fungoides with intermittent low-dose gemcitabine. Oncology 2007;73:130-135.

Pentostatin

Cummings FJ, Kim K, Neiman RS, et al. Phase II trial of pentostatin in refractory lymphomas and cutaneous T-cell disease. J Clin Oncol 1991;9:565-571.

Temozolomide

Tani M, Fina M, Alinari L, Stefoni V, Baccarani M, Zinzani PL. Phase II trial of temozolomide in patients with pretreated cutaneous T-cell lymphoma. Haematologica 2005;90(9):1283-1284.

Querfeld C, Rosen ST, Guitart J, et al. Multicenter phase II trial of temozolomide in mycosis fungoides/sezary syndrome: correlation with O^6-methylguanine-DNA methyltransferase and mismatch repair proteins. Clin Cancer Res 2011;17:5748-5754.

Low-dose Pralatrexate

Horwitz SM, Kim YH, Foss F, et al. Identification of an active, well-tolerated dose of pralatrexate in patients with relapsed or refractory cutaneous T-cell lymphoma (CTCL). Blood 2012;119:4115-4122.

Pralatrexate

O'Connor OA, Pro B, Pinter-Brown L, et al. Pralatrexate in patients with relapsed or refractory Peripheral T-cell lymphoma: Results from the pivotal PROPEL study. J Clin Oncol 2011;29:1182-1189.

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Combination Therapies
Skin-directed + Systemic
Rupoli S, Goteri G, Pulini S, et al. Long term experience with low dose interferon alpha and PUVA in the management of early mycosis fungoides. Eur J Haematol 2005;75:136-145.

Kuzel TM, Roenigk HH Jr, Samuelson E, et al. Effectiveness of interferon alfa-2a combined with phototherapy for mycosis fungoides and the Sézary syndrome. J Clin Oncol 1995;13:257-263.

McGinnis KS, Shapiro M, Vittorio CC, et al. Psoralen plus long wave UV A (PUVA) and bexarotene therapy: An effective and synergistic combined adjunct to therapy for patients with advanced cutaneous T cell lymphoma. Arch Dermatol 2003;139:771-775.

Wilson LD, Jones GW, Kim D, et al. Experience with total skin electron beam therapy in combination with extracorporeal photopheresis in the management of patients with erythrodermic (T4) mycosis fungoides. J Am Acad Dermatol 2000;43:54-60.

Stadler R, Otte H-G, Luger T, et al. Prospective randomized multicenter clinical trial on the use of interferon alpha -2a plus acitretin versus interferon alpha -2a plus PUVA in patients with cutaneous T-cell lymphoma stages I and II. Blood 1998;92:3578-3581.

Systemic + Systemic
Straus DJ, Duvic M, Kuzel T, et al. Results of a phase II trial of oral bexarotene (Targretin) combined with interferon alfa 2b (Intron A) for patients with cutaneous T cell lymphoma. Cancer 2007;109:1799-1803.

Talpur R, Ward S, Apisarnthanarax N, Breuer Mcham J, Duvic M. Optimizing bexarotene therapy for cutaneous T cell lymphoma. J Am Acad Dermatol 2002;47:672-684.

Suchin KR, Cucchiara AJ, Gottleib SL, et al. Treatment of cutaneous T-cell lymphoma with combined immunomodulatory therapy: a 14-year experience at a single institution. Arch Dermatol. 2002;138:1054-1060.

Raphael BA, Shin DB, Suchin KR, et al. High clinical response rate of Sezary syndrome to immunomodulatory therapies: prognostic markers of response. Arch Dermatol 2011;147:1410-1415.

Allogeneic stem cell transplant
Duarte RF, Canals C, Onida F, et al. Allogeneic hematopoietic cell transplantation for patients with mycosis fungoides and Sezary syndrome: A retrospective analysis of the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 2010;28:4492-4499.

Duarte RF, Schmitz N, Servitje O, Sureda A. Haematopoietic stem cell transplantation for patients with primary cutaneous T-cell lymphoma. Bone Marrow Transplant 2008;41:597-604.

Duvic M, Donato M, Dabaja B, et al. Total skin electron beam and non-myeloablative allogeneic hematopoietic stem-cell transplantation in advanced mycosis fungoides and Sezary syndrome. J Clin Oncol 2010;28:2365-2372.

Molina A, Zain J, Arber DA, et al. Durable clinical, cytogenetic, and molecular remissions after allogeneic hematopoietic cell transplantation for refractory Sezary syndrome and mycosis fungoides. J Clin Oncol 2005;23:6163-6171.

Wu PA, Kim YH, Lavori PW, Hoppe RT, Stockerl-Goldstein KE. A meta-analysis of patients receiving allogeneic or autologous hematopoietic stem cell transplant in mycosis fungoides and Sezary syndrome. Biol Blood Marrow Transplant 2009;15:982-990.

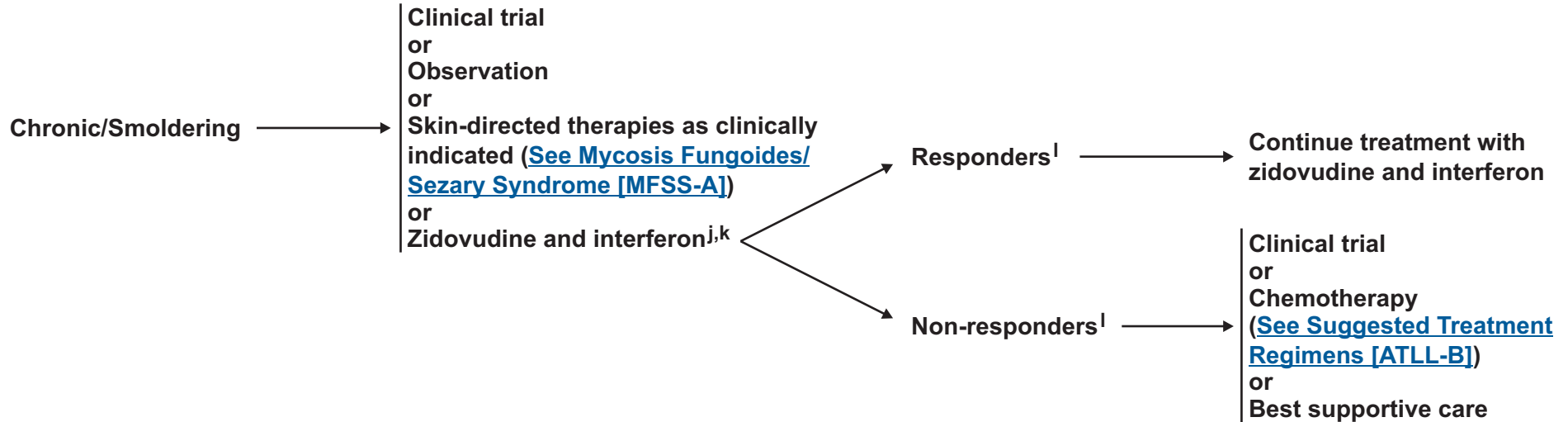**Note:** All recommendations are category 2A unless otherwise indicated.
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SUPPORTIVE CARE FOR MF/SS

Pruritus

- **Assessment**
  - ➤ **Pruritus should be assessed at each visit using consistent measurements**
  - ➤ **Generalized pruritus and localized pruritus should be distinguished**
  - ➤ **Correlation between sites of disease and localization of pruritus should be noted**
  - ➤ **Other potential causes for pruritus should be ruled out**

- **Treatment**
  - ➤ **Moisturizers, emollients, and barrier protection**
  - ➤ **Topical steroid (appropriate strength for body region) ± occlusion**
  - ➤ **Optimize skin-directed and systemic therapy**
  - ➤ **Topical preparations - camphor/menthol formulations, pramoxine formulations**
  - ➤ **Systemic agents**
    - ◊ **First-line**
      - - Antihistamines
      - - Doxepin
      - - Gabapentin
    - ◊ **Second-line**
      - - Aprepitant
      - - Mirtazapine
      - - Selective serotonin reuptake inhibitors
    - ◊ **Third-line**
      - - Naltrexone

Infections

- **Active or Suspected Infections**
  - ➤ **Erythroderma:**
    - ◊ **Skin swab and nares cultures for Staphylococcus aureus (S. aureus) infection or colonization**
    - ◊ **Intranasal mupirocin**
    - ◊ **Oral dicloxacillin or cephalexin**
    - ◊ **Sulfamethoxazole/trimethoprim, doxycycline if suspect MRSA**
    - ◊ **Vancomycin if no improvement or bacteremia**
    - ◊ **Bleach baths or soaks (if limited area)**
  - ➤ **Ulcerated and necrotic tumors:**
    - ◊ **Gram-negative rods (GNR) common in necrotic tumors may lead to bacteremia and sepsis**
    - ◊ **If high suspicion for infection, obtain blood cultures, start antibiotics even if fever absent**
    - ◊ **Role of wound cultures not clear due to colonization**
    - ◊ **Empirical therapy for both GNR and gram-positive coccal infections is necessary initially**
- **Prophylaxis**
  - ➤ **Optimize skin barrier protection**
  - ➤ **Mupirocin for S. aureus colonization**
  - ➤ **Bleach baths or soaks (if limited area)**
  - ➤ **Avoid central lines (especially in erythrodermic patients)**
  - ➤ **For patients receiving alemtuzumab, see NHODG-B.**

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OVERVIEW & DEFINITION

- **Primary cutaneous CD30+ T-cell lymphoproliferative disorders (LPDs) represent a spectrum that includes primary cutaneous ALCL, lymphomatoid papulosis, and "borderline" cases with overlapping clinical and histopathologic features.[a,b]**
- **Clinical correlation with histopathologic features is <u>essential</u> for establishing the diagnosis of primary cutaneous CD30+ T-cell LPDs; diagnosis cannot be made based on pathology review alone.**

Differential diagnosis
- **It is critical to distinguish CD30+ T-cell LPDs from other CD30+ processes involving the skin that include:**
  - ➤ **Systemic lymphomas (eg, systemic ALCL, ATLL, PTCL),**
  - ➤ **Other cutaneous process such as other CD30+ skin lymphomas such as mycosis fungoides (MF), especially transformed MF, cytotoxic T-cell lymphomas, and**
  - ➤ **Benign disorders such as lymphomatoid drug reactions, arthropod bites, viral infections and others.**
- **Lymphomatoid drug reactions has been linked with certain drugs (eg, amlodipine, carbamazepine, cefuroxime, valsartan) and is associated with CD30+ atypical large cells in histology**
- **MF and primary cutaneous CD30+ T-cell LPD can coexist in the same patient.**

- **Primary cutaneous ALCL (PC-ALCL)**
  - ➤ **Represents about 8% of cutaneous lymphoma cases.[b]**
  - ➤ **Unlike systemic ALCL, PC-ALCL typically follows an indolent course and although cutaneous relapses are common an excellent prognosis is usually maintained.[c]**
  - ➤ **Histologically characterized by diffuse, cohesive sheets of large CD30-positive (in >75%) cells with anaplastic, pleomorphic, or immunoblastic appearance.[a,b]**
  - ➤ **Clinical features typically include solitary or localized nodules or tumors (often ulcerated); multifocal lesions occur in about 20% of cases. Extracutaneous disease occurs in about 10% of cases, usually involving regional lymph nodes.[a,b]**
  - ➤ **Except in rare cases, PC-ALCL is ALK-**

- **Lymphomatoid papulosis (LyP)**
  - ➤ **LyP has been classified (WHO-EORTC) under lymphomas but may be best classified as a LPD as it is a uniformly spontaneously regressing process.[b]**
  - ➤ **LyP has been reported to be associated with other lymphomas such as MF, PC-ALCL, systemic ALCL, or Hodgkin lymphoma.[d,e]**
  - ➤ **Histologically heterogenous with large atypical anaplastic, immunoblastic, or Hodgkin-like cells in a marked inflammatory background;[a] several histologic subtypes (types A to D, with CD30-positive cells) defined based on evolution of skin lesions.[d]**
  - ➤ **Clinical features characterized by chronic, recurrent spontaneously regressing papulonodular (grouped or generalized) skin lesions.[a,b,d]**

See Diagnosis (PCTLD-2)

[a]Ralfkiaer E, Willemze R, Paulli M, Kadin ME. Primary cutaneous CD30-positive T-cell lymphoproliferative disorders. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:300-301.
[b]Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005;105:3768-3785.
[c]Benner MF, Willemze R. Applicability and prognostic value of the new TNM classification system in 135 patients with primary cutaneous anaplastic large cell lymphoma. Arch Dermatol 2009;145:1399-1404.

[d]Kempf W, Pfaltz K, Vermeer MH, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Blood 2011;118:4024-4035.
[e]Due to overlapping immunophenotype and morphology, need to use caution to *not* diagnose CD30+ T-cell in lymph nodes as HL (Eberle FC, Song JY, Xi L, et al. Nodal involvement by cutaneous CD30-positive T-cell lymphoma mimicking classical Hodgkin lymphoma. Amer J Surg Pathol 2012;36:716-725.)

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DIAGNOSIS

ESSENTIAL:
- **Clinical presentation: see Overview and Definition**
- **Clinical pathologic correlation is essential**
- **Complete skin examination for evidence of MF**
- **Biopsy of suspicious skin sites**
  - ➤ **Histopathology review of adequate biopsy (punch, incisional, excisional).**
  - ➤ **Review of all slides with at least one paraffin block representative of the tumor should be done by a pathologist with expertise in the diagnosis of cutaneous T-cell lymphoma. Rebiopsy if consult material is nondiagnostic.**
- **Adequate immunophenotyping to establish diagnosis[f,g] on skin biopsy:**
  - ➤ **IHC: CD3, CD4, CD8, CD20, CD30, CD56, βF1, ALK1[h]**

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- **On skin biopsy:**
  - ➤ **Expanded IHC: CD2, CD5, CD7, CD25, TIA1, granzyme B, perforin, GM1, EBER-ISH**
  - ➤ **Molecular analysis to detect: gene rearrangements: TCR[i] (assessment of clonality)**
- **Excisional or incisional biopsy of suspicious lymph nodes (in absence of definitive skin diagnosis)**
- **Assessment of HTLV-1 serology in at-risk populations to identify CD30+ ATLL**

- **Cutaneous anaplastic large cell lymphoma (ALCL)**
- **Lymphomatoid papulosis (LyP)[j]**
→ **See Workup (PCTLD-3)**

CD30+ transformed mycosis fungoides → **See Mycosis Fungoides Guidelines (MFSS-1)**

[g]See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).
[g]Typical immunophenotype: CD30+ (>70% cells),CD4+ variable loss of CD2/CD5/CD3,CD8+ (<5%) cytotoxic granule proteins positive.
[h]ALK1 positivity and t(2;5) translocation is typically absent in PC-ALCL and LyP.
[i]TCR gene rearrangement results should be interpreted with caution. TCR clonal rearrangement can be seen in non-malignant conditions or may not be demonstrated in all cases of MF/SS. Demonstration of identical clones in skin, blood, and/or lymph node may be helpful in selected cases.
[j]LyP is not considered a malignant disorder; however, there is an association with other lymphoid malignancy (mycosis fungoides, classical Hodgkin lymphoma, or PC-ALCL) and staging studies are only done to rule out suspicion of systemic disease.

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WORKUP

Cutaneous ALCL →

ESSENTIAL:
- Complete physical examination including entire skin;[k] palpation of peripheral lymph node regions; liver or spleen enlargement
- CBC, differential
- Comprehensive metabolic panel
- LDH
- Chest/abdominal/pelvic contrast-enhanced CT or integrated whole body PET-CT
- Biopsy suspicious nodes[e,l,m]

USEFUL IN SELECTED CASES:
- Pregnancy testing in women of child-bearing age[n]
- Bone marrow aspiration and biopsy optional for solitary C-ALCL or C-ALCL without extracutaneous involvement on imaging

Primary cutaneous ALCL → See Primary Treatment (PCTLD-4)

Cutaneous ALCL with regional node → See Primary Treatment (PCTLD-4)

Systemic ALCL → See Peripheral T-cell Lymphoma (TCEL-1)

LyP[j] →

ESSENTIAL:
- Complete physical examination including entire skin;[k] palpation of peripheral lymph node regions; liver or spleen enlargement
- CBC, differential
- Comprehensive metabolic panel
- LDH

USEFUL IN SELECTED CASES:
- Pregnancy testing in women of child-bearing age[n]
- Chest/abdominal/pelvic contrast-enhanced CT or integrated whole body PET-CT[j,o]
- Bone marrow aspiration and biopsy (not done for typical LyP)[j,o]

→ See Primary Treatment for LyP (PCTLD-5)

[e] Due to overlapping immunophenotype and morphology, need to use caution to *not* diagnose CD30+ T-cell in lymph nodes as HL (Eberle FC, Song JY, Xi L, et al. Nodal involvement by cutaneous CD30-positive T-cell lymphoma mimicking classical Hodgkin lymphoma. Amer J Surg Pathol 2012;36:716-725.)

[j] LyP is not considered a malignant disorder; however, there is an association with other lymphoid malignancy (mycosis fungoides, classical Hodgkin lymphoma, or PC-ALCL). Staging studies are done in LyP only if there is suspicion of systemic involvement by an associated lymphoma.

[k] Monitoring the size and number of lesions will assist with response assessment.

[l] Consider systemic ALCL, regional lymph node involvement with PC-ALCL, or lymph node involvement with transformed MF.

[m] Consider PC-ALCL if in draining lymph nodes only.

[n] Many skin-directed and systemic therapies are contraindicated or of unknown safety in pregnancy. Refer to individual drug information.

[o] Only done to exclude an associated lymphoma.

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SUBTYPE	EXTENT OF DISEASE	PRIMARY TREATMENT	FOLLOW-UP[s]	RELAPSE/REFRACTORY DISEASE

Primary cutaneous ALCL[p]

Solitary or grouped lesions → Surgical excision ± RT[q] or RT[q]

- Response → Observe for recurrence →
  - **Retreat with initial treatment if disease confined to skin**
  - **For multifocal lesions or extracutaneous involvement, see below**
- No response/refractory →

Multifocal lesions → Methotrexate (≤100 mg weekly) or RT[q] or Systemic retinoids[r] or Pralatrexate or Observation, if asymptomatic or Interferon alpha (category 2B)

- Response[t] → Observe for recurrence →
- No response/refractory →

Cutaneous ALCL with regional node (excludes systemic ALCL) → Methotrexate ± RT[q] or Pralatrexate ± RT[q] or CHOP or CHOEP ± RT[q] in selected cases or RT[q] in selected cases

- Response → Observe for recurrence →
- No response/refractory →

Relapse/Refractory Disease options:
- **Clinical trial**
- **Treat with same (unless refractory or intolerant) regimen**
- **Alternative regimen not used for primary treatment**
- **Mycosis fungoides "Category C Systemic Therapies" (SYST-CAT C) (See MFSS-A)**

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[p]Regression of lesions may occur in up to 44% of cases.
[q]See Principles of Radiation Therapy (NHODG-D).
[r]Limited data from case reports (eg, bexarotene).
[s]Mycosis fungoides can develop over time; continue to conduct thorough skin exam during follow-up.

[t]Patients achieving a response and/or a clinical benefit with cutaneous disease should be considered for maintenance or taper regimens to optimize response duration. Patients who relapse often respond well to the same treatment. Patients with a PR should be treated with the other options in the primary treatment list to improve response before moving onto treatment for refractory disease. Patients with relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

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Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders

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SUBTYPE	EXTENT OF DISEASE	PRIMARY TREATMENT	FOLLOW-UP[v]		RELAPSE/REFRACTORY DISEASE
LyP	Limited lesions or asymptomatic	Observation (preferred for asymptomatic) or Topical steroids or Phototherapy	Asymptomatic disease	→ Continue observation or Topical steroids
			Symptomatic disease	→ Treat with alternative regimen not used for primary treatment or Other regimens
	Extensive lesions or symptomatic	Observation or Methotrexate [10-35 mg weekly[u]) or Phototherapy or Systemic retinoids[r] or Topical steroids or Topical nitrogen mustard	Response[w] → Observe for recurrence	Clinical trial or Observation or Retreat or treat with alternative regimen not used for primary treatment
			No response/ refractory	
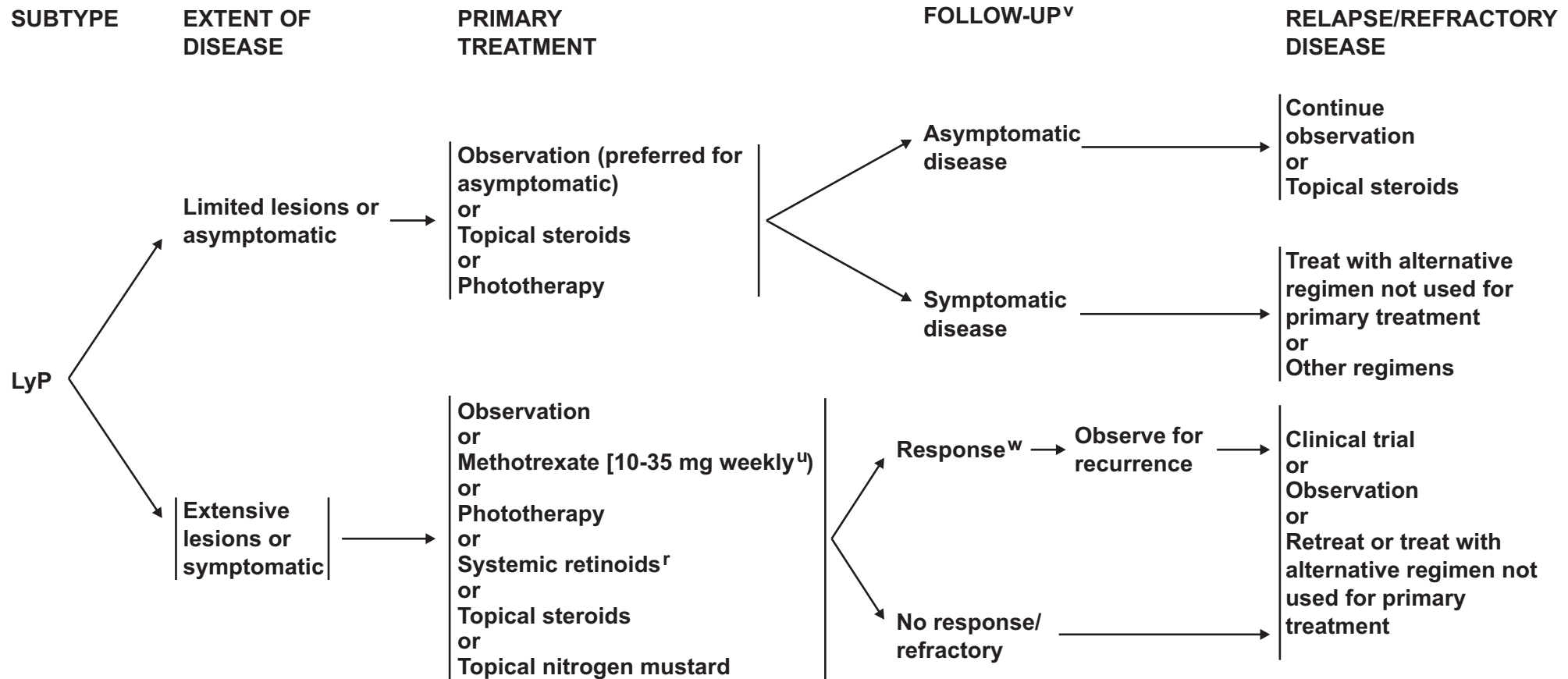
[r] Limited data from case reports (eg, bexarotene).

[u] Kempf W, Pfaltz K, Vermeer MH, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Blood 2011;118:4024-4035.

[v] Life-long follow up is warranted due to high risks for second lymphoid malignancies; continue to conduct thorough skin exam during follow-up.

[w] Patients achieving a response and/or a clinical benefit may be considered for maintenance or taper regimens to optimize response duration. Patients who relapse often respond well to the same treatment. Patients with a PR should be treated with the other options in the primary treatment list to improve response before moving onto treatment for refractory disease. Patients with relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

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DIAGNOSIS

ESSENTIAL: [a,b]

- Peripheral blood smear analysis for cytology; presence of larger lymphocytes characterized by reniform or round nucleus and abundant cytoplasm containing azurophilic granules
- Flow cytometry on peripheral blood
- Bone marrow aspirate and biopsy [c]
- Adequate immunophenotyping to establish diagnosis [d]
  - Cell surface marker analysis by flow cytometry: CD3, CD4, CD5, CD7, CD8, CD16, CD56, CD57, CD28, TCRαβ, TCRγδ, CD45RA, CD62L
  - IHC panel: CD3, CD4, CD5, CD7, CD8, CD56, CD57, EBER, TCRβ, TCRγ, TIA1, granzyme B, granzyme M
- Molecular analysis to detect gene rearrangement: [e] TCRβ, TCRγ

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- Flow cytometry to assess clonality: TCR Vβ
- Mutational analysis: STAT3 and STAT5B

WORKUP

ESSENTIAL:
- History and physical examination: evaluation of enlarged spleen, liver; presence of lymphadenopathy (rare)
- Presence of autoimmune disease [a] (especially rheumatoid arthritis [RA])
- Performance status
- CBC, differential, platelets
- Comprehensive metabolic panel
- Serologic studies: HIV-1,2, HTLV-1,2,
- PCR for viral DNA or RNA: HBV, HCV, EBV, CMV

USEFUL IN SELECTED CASES:
- Serological markers (eg, RF, ANA, ESR) for autoimmune disease
- Ultrasound of liver/spleen
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Echocardiography [f]

→ T-LGL leukemia → See Indication for Treatment (LGLL-2)

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[a] Autoimmune disorders such as rheumatoid arthritis can occur in patients with T-cell large granular lymphocytic leukemia (LGL). Small, clinically non-significant clones of T-cell LGLs can be detected concurrently in patients with bone marrow failure disorders.

[b] Rule out reactive LGL lymphocytosis. Repeat peripheral blood flow cytometry and TCR gene rearrangement studies in 6 months in asymptomatic patients with small clonal LGL populations ($<0.5 \times 10^9$/L) or polyclonal LGL lymphocytosis.

[c] Typically needed to confirm diagnosis; essential for cases with low T-LGL counts ($<0.5 \times 10^9$/L) and cases suspicious for concurrent bone marrow failure disorders.

[d] Typical immunophenotype for T-LGL: CD3+ CD8+ CD16+ CD57+ CD56- CD28- CD5 dim and/or CD7 dim CD45RA+ CD62L- TCRαβ+ TIA1+ granzyme B+ granzyme M+.

[e] TCR gene rearrangement results should be interpreted with caution. Clonal TCR gene rearrangement without cytologic and immunophenotypic evidence of abnormal T-cell population does not constitute a diagnosis of T-cell malignancy since it can be seen in healthy subjects.

[f] In patients with unexplained shortness of breath and/or right heart failure.

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T-cell Large Granular Lymphocytic Leukemia

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INDICATION FOR TREATMENT

FIRST-LINE THERAPY

RESPONSE (at 4 mo)

FOLLOW-UP

SECOND-LINE THERAPY

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

- ANC $<0.5 \times 10^9$/L
- Hemoglobin <10 g/dL or need for RBC transfusion
- Platelets $<50 \times 10^9$/L
- Autoimmune conditions requiring therapy (typically RA)
- Symptomatic splenomegaly
- Severe B symptoms
- Pulmonary artery hypertension

No indication → **Observe**

Indication present → Low-dose methotrexate ± corticosteroids[g] or Cyclophosphamide ± corticosteroids[g] or Cyclosporine[g]

→ **CR/PR**[h,i] → Continue with initial treatment

→ **No response**[i] → Continue with alternate first-line therapy

No response or progressive or refractory disease to all first-line therapies →
- Clinical trial
- Purine analogues[j]
- Alemtuzumab
- Splenectomy

CR/PR[i] → See above

---

[g]Methotrexate with or without steroids may be beneficial in patients with autoimmune disease; cyclophosphamide or cyclosporine may be used as a first- or second-line option in patients with anemia. Lamy T, Loughran TP Jr. How I treat LGL leukemia. Blood 2011;117(10):2764-74.

[h]Complete response is defined as: recovery of blood counts to Hgb >12 g/dL, ANC $>1.5 \times 10^9$/L, platelet $>150 \times 10^9$/L), resolution of lymphocytosis ($<4 \times 10^9$/L) and circulating LGL counts within normal range ($<0.5 \times 10^9$/L). Partial response is defined as: recovery of hematologic parameters to Hgb >8 g/dL, ANC $>0.5 \times 10^9$/L, platelet $>50 \times 10^9$/L and absence of transfusions. Bareau B, Rey J, Hamidou M, et al. Analysis of a French cohort of patients with large granular lymphocyte leukemia: a report on 229 cases. Hematologica 2010;95:1534-1541.

[i]Limit therapy with cyclophosphamide to 4 mo if no response and to ≤12 mo if PR observed at 4 mo due to increased risk of leukemogenesis.

[j]Pentostatin, cladribine, and fludarabine have been used in LGL.

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DIAGNOSIS

WORKUP

DIAGNOSTIC CATEGORY[d]

ESSENTIAL:[a]
- **HTLV-1 serology:[b] ELISA and confirmatory western blot if ELISA is positive. If western blot is indeterminate, then HTLV-1 PCR can be performed.**
- **CBC and peripheral blood smear for atypical cells:[c] lymphocytosis (ALC >4000/μL in adults) in acute and chronic subtypes[d]**
- **Flow cytometry on peripheral blood[e]**

USEFUL IN CERTAIN CIRCUMSTANCES:
- **Biopsy of lymph nodes (excisional), skin biopsy, GI tract, or bone marrow biopsy[f] is required if:**
  - ▸ **Diagnosis is not established on peripheral blood, or**
  - ▸ **Ruling out an underlying infection (tuberculosis, histoplasmosis, toxoplasmosis, etc.)**
  - ▸ **If biopsy performed, the recommended panel for paraffin section immunohistochemistry:[g,h] CD3, CD4, CD5, CD7, CD8, CD25, CD30**

ESSENTIAL:
- **Complete H&P examination, including complete skin exam**
- **Electrolytes, BUN, creatinine, serum calcium, serum LDH**
- **Chest/abdominal/pelvic/neck CT scan**
- **Pregnancy testing in women of child-bearing age (if chemotherapy planned)**

USEFUL IN SELECTED CASES:
- **Upper gastrointestinal endoscopy**
- **Skeletal survey in symptomatic patients**
- **Stool examination for parasites (strongyloides is most likely)**
- **PET-CT scan**
- **Central nervous system evaluation: CT scan, MRI and/or lumbar puncture in all patients with acute or lymphoma subtypes or in patients with neurologic manifestations**

See First-Line Therapy for Chronic/Smoldering Subtype (ATLL-2)

See First-Line Therapy for Acute Subtype (ATLL-3)

See First-Line Therapy for Lymphoma (ATLL-3)

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[a] The diagnosis of ATLL requires histopathology and immunophenotyping of tumor lesion, *or* morphology and immunophenotying of peripheral blood, *and* HTLV-1 serology.

[b] See map for prevalence of HTLV-1 by geographic region.

[c] Typical ATL cells ("flower cells") have distinctly polylobated nuclei with homogeneous and condensed chromatin, small or absent nucleoli, and agranular and basophilic cytoplasm, but multiple morphologic variations can be encountered. Presence of ≥5% atypical cells by morphology in peripheral blood is required for diagnosis in the absence of other criteria.

[d] Shimoyama M and members of The Lymphoma Study Group. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the Lymphoma Study Group (1984-87). Br J Haematol 1991;79:428-437.

[e] Typical immunophenotype: CD2+ CD3+ CD4+ CD5+ CD7- CD8- CD25+ CD30-/+ TCRαβ+. Presence of ≥5% T-lymphocytes with an abnormal immunophenotype in peripheral blood is required for diagnosis.

[f] Bone marrow involvement is an independent poor prognostic factor.

[g] See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).

[h] Usually CD4+ T-cells with expression of CD2, CD5, CD25, CD45RO, CD29, T-cell receptor αβ, and HLA-DR. Most cases are CD7- and CD26- with low CD3 expression. Rare cases are CD8+ or CD4/CD8 double positive or double negative.

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Adult T-Cell Leukemia/Lymphoma

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ATLL SUBTYPE[d]	FIRST-LINE THERAPY[i]	INITIAL RESPONSE (at 2 mo)	Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

Chronic/Smoldering →

Clinical trial
or
Observation
or
Skin-directed therapies as clinically indicated (See Mycosis Fungoides/ Sezary Syndrome [MFSS-A])
or
Zidovudine and interferon[j,k]

→ **Responders[l]** → **Continue treatment with zidovudine and interferon**

→ **Non-responders[l]** → **Clinical trial**
or
Chemotherapy (See Suggested Treatment Regimens [ATLL-B])
or
Best supportive care

[d] Shimoyama M and members of The Lymphoma Study Group. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the Lymphoma Study Group (1984-87). Br J Haematol 1991;79:428-437.

[i] Supportive care: anti-infectious prophylaxis with sulfamethoxazole/trimethoprim + strongyloidosis is recommended.

[j] Outside of a clinical trial, if a patient is not responding or is progressing, treatment with zidovudine and interferon should be stopped. If there is evidence of clinical benefit, treatment should continue until best response is achieved. If life-threatening manifestations, treatment can be discontinued before the 2-month period.

[k] See references for zidovudine and interferon (ATLL-C).

[l] See Response Criteria for ATLL (ATLL-A). Responders include CR, uncertified PR, and PR.

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ATLL SUBTYPE[d] **FIRST-LINE THERAPY[i]** **INITIAL RESPONSE (after 2 cycles)**

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

Acute[m] →

Clinical trial
or
Zidovudine and interferon[j,k]
or
Chemotherapy
(See Suggested Treatment Regimens [ATLL-B])

Responders[l] →

Continue prior therapy
or
Consider allogeneic stem cell transplant

Non-responders[l] →

Clinical trial
or
Best supportive care
or
Alternate therapy not previously treated with:
• See ATLL-B or See TCEL-B for Second-line therapy
or
• Zidovudine and interferon

→ **Responders[l]** → Consider allogeneic stem cell transplant

Lymphoma[m,n,o] →

Clinical trial
or
Chemotherapy
(See Suggested Treatment Regimens [ATLL-B])

Responders[l] →

Continue chemotherapy
or
Consider allogeneic stem cell transplant

Non-responders[l] →

Clinical trial
or
Best supportive care
or
Chemotherapy (See TCEL-B for Second-line therapy)

→ **Responders[l]** → Consider allogeneic stem cell transplant

[d] Shimoyama M and members of The Lymphoma Study Group. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the Lymphoma Study Group (1984-87). Br J Haematol 1991;79:428-437.

[i] Supportive care: anti-infectious prophylaxis with sulfamethoxazole/trimethoprim + strongyloidosis is recommended.

[j] Outside of a clinical trial, if a patient is not responding or is progressing, treatment with zidovudine and interferon should be stopped. If there is evidence of clinical benefit, treatment should continue until best response is achieved. If life-threatening manifestations, treatment can be discontinued before the 2-month period.

[k] See References for zidovudine and interferon (ATLL-C).

[l] See Response Criteria for ATLL (ATLL-A). Responders include CR, uncertified PR, and PR.

[m] Efficacy of long-term treatment is limited. There are small series where transplant is beneficial. There is no defined treatment.

[n] Antiviral therapy is not effective.

[o] CNS prophylaxis: intrathecal chemotherapy is recommended (methotrexate and cytarabine and corticosteroids).

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RESPONSE CRITERIA FOR ATLL[a]

Response	Definition	Lymph Nodes	Extranodal Masses	Spleen, Liver	Skin	Peripheral Blood	Bone Marrow
Complete remission*	Disappearance of all disease	Normal	Normal	Normal	Normal	Normal[†]	Normal
Uncertified complete remission*	Stable residual mass in bulky lesion	≥75% decrease[‡]	≥75% decrease[‡]	Normal	Normal	Normal[†]	Normal
Partial remission*	Regression of disease	≥50% decrease[‡]	≥50% decrease[‡]	No increase	≥50% decrease	≥50% decrease	Irrelevant
Stable disease*	Failure to attain complete/partial remission and no progressive disease	No change in size	No change in size	No change in size	No change in size	No change	No change
Relapsed disease or progressive disease	New or increased lesions	New or ≥50% increase[§]	New or ≥50% increase[§]	New or ≥50% increase	≥50% increase	New or ≥50% increase[#]	Reappearance

*Required that each criterion be present for a period of at least 4 weeks.

[†]Provided that <5% of flower cells remain, complete remission is judged to have been attained if the absolute lymphocyte count, including flower cells, is <4 x 10^9/L.

[‡]Calculated by the sum of the products of the greatest diameters of measurable disease.

[§]Defined by ≥50% increase from nadir in the sum of the products of measurable disease.

[#]Defined by ≥50% increase from nadir in the count of flower cells and an absolute lymphocyte count, including flower cells, of >4 x10^9/L.

[a]Tsukasaki K, Hermine O, Bazarbachi A, et al. Definition, prognostic factors, treatment, and response criteria of adult T-cell leukemia-lymphoma: A proposal from an international consensus meeting. J Clin Oncol 2009;27:453-459.

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SUGGESTED TREATMENT REGIMENS

- **Chemotherapy^a (alphabetical order)**
  - ➤ **CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)**
  - ➤ **CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone)**
  - ➤ **Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)**
  - ➤ **HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine**

^aThere are no published data regarding the use of these regimens; however, they are used at NCCN Member Institutions for the treatment of ATLL.

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REFERENCES FOR ZIDOVUDINE AND INTERFERON

Zidovudine and interferon

Bazarbachi A, Hermine O. Treatment with a combination of zidovudine and alpha-interferon in naive and pretreated adult T-cell leukemia/lymphoma patients. J Acquir Immune Defic Syndr Hum Retrovirol 1996;13 Suppl 1:S186-190.

Bazarbachi A, Plumelle Y, Carlos Ramos J, et al. Meta-analysis on the use of zidovudine and interferon-alfa in adult T-cell leukemia/lymphoma showing improved survival in the leukemic subtypes. J Clin Oncol 2010;28:4177-4183.

Hermine O, Allard I, Levy V, Arnulf B, Gessain A, Bazarbachi A. A prospective phase II clinical trial with the use of zidovudine and interferon-alpha in the acute and lymphoma forms of adult T-cell leukemia/lymphoma. Hematol J 2002;3:276-282.

Hodson A, Crichton S, Montoto S, et al. Use of zidovudine and interferon alfa with chemotherapy improves survival in both acute and lymphoma subtypes of adult T-cell leukemia/lymphoma. J Clin Oncol 2011;29:4696-4701.

White JD, Wharfe G, Stewart DM, et al. The combination of zidovudine and interferon alpha-2B in the treatment of adult T-cell leukemia/lymphoma. Leuk Lymphoma 2001;40:287-294.

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NCCN Guidelines Version 4.2014
Extranodal NK/T-Cell Lymphoma, nasal type

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DIAGNOSIS[a]

ESSENTIAL:
- Hematopathology review of all slides with a least one paraffiin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- A FNA or core needle biopsy alone is not suitable for the initial diagnosis of lymphoma.[b]
- In certain circumstances, when tissue is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for antigen receptor rearrangements, and FISH for major translocations) may be sufficient for diagnosis.
- Adequate immunophenotyping to establish diagnosis[c,d]
  ➤ IHC panel: For high clinical suspicion of NKTL, first panel should include: cCD3ε, CD56, EBER-ISH[e]

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- Molecular analysis to detect: TCR gene rearrangement
- IHC panel:
  ➤ B-cell lineage: CD20
  ➤ T-cell lineage: CD2, CD7, CD8, CD4, CD5
  ➤ Other: CD30, Ki-67

[a]It is preferred that treatment occur at centers with expertise in the management of this disease.

[b]Necrosis is very common in diagnostic biopsies and may delay diagnosis significantly. Biopsy should include the edges of lesions to increase the odds of having viable tissue. Useful to perform multiple nasopharyngeal biopsies even in areas not clearly involved.

[c]See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).

[d]Typical NK-cell immunophenotype: CD20-, CD2+, cCD3ε+ (surface CD3-), CD4-, CD5-, CD7-/+, CD8-/+, CD43+, CD45RO+, CD56+, T-cell receptor (TCR)αβ-, TCRγδ-, EBV-EBER+. TCR and Ig genes are germline (NK lineage). Cytotoxic granule proteins (TIA1, Perforin, Granzyme B) are usually expressed. Typical T-cell immunophenotype: CD2+ sCD3+ cCD3e+, CD4,5,7,8 variable, CD56+/- EBV-EBER+ TCRαβ or γδ+, cytotoxic granule proteins +. TCR genes are clonally rearranged.

SUBTYPES

Subtypes included:
- Extranodal NK/T-cell, nasal type

Subtypes _not_ included:
- NK-cell leukemias
- Precursor NK-cell neoplasm

WORKUP

ESSENTIAL:
- Physical exam: attention to complete ENT evaluation nasopharynx involvement (including Waldeyer's ring), testicles, and skin
- Performance status
- B symptoms
- CBC, differential platelets
- LDH
- Comprehensive metabolic panel
- Uric acid
- Bone marrow biopsy + aspirate[f]
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- PET scan
- Dedicated CT or MRI of the nasal cavity, hard palate, anterior fossa, nasopharynx
- Calculation of NK/T-cell PI[g]
- MUGA scan/echocardiogram if treatment includes regimens containing anthracyclines or anthracenedione
- EBV viral load[h]
- Concurrent referral to RT for pre-treatment evaluation

USEFUL IN SELECTED CASES:
- Pregnancy testing in women of child-bearing age
- Discussion of fertility and sperm banking
- HIV

[e]Negative result should prompt pathology review for alternative diagnosis.

[f]BM aspirate - lymphoid aggregates are rare, and are considered involved if EBER-1 positive; hemophagocytosis may be present.

[g]See NK/T-cell Lymphoma Prognostic Index (NKTL-A).

[h]EBV viral load is important in diagnosis and possibly in monitoring of disease. A positive result is consistent with NK/T-cell, nasal type. Lack of normalization of EBV viremia should be considered indirect evidence of persistent disease.

See Induction Therapy (NKTL-2)

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STAGE

INDUCTION THERAPY

Nasal

Stage I → Assess risk factors

No risk factors present →
Clinical trial
or
RT alone[i]
or
Concurrent chemoradiation[i]
or
Sequential chemoradiation[i]

Presence of ANY risk factor →
Clinical trial
or
Concurrent chemoradiation[i]
or
Sequential chemoradiation[i]

Stage II →

See Post-RT Evaluation (NKTL-3)

Stage IV →
Clinical trial
or
Concurrent chemoradiation[i]
or
Combination chemotherapy regimen (pegaspargase-based)[i] ± RT[i]

Extranasal → Stage I, II, IV →

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

Adapted with permission from Kohrt H, Lee M, Advani R. Risk stratification in extranodal natural killer/T-cell lymphoma. Expert Rev Anticancer Ther 2010;10:1395-1405.
[i] See Suggested Treatment Regimens (NKTL-B).

Risk factors
(includes elements of NK/T-cell Lymphoma PI on NKTL-A)

- Age >60 y
- B symptoms
- ECOG PS ≥2
- Elevated LDH
- Regional node involvement

- Local tumor invasion (LTI); bone or skin
- Histologic evidence of high Ki-67 staining
- EBV DNA titer $\geq 6.1 \times 10^7$ copies/mL

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POST RT EVALUATION

RESPONSE TO THERAPY[k]

ADDITIONAL THERAPY

Post-RT evaluation[j]
- **Repeat initial imaging of CT, MRI, or PET-CT scan**
- **Endoscopy with visual inspection and repeat biopsies**
- **EBV viral load**

Nasal

Stage I, with or without risk factors

CR[l] → **Observe**

PR → **Hematopoietic stem cell transplant (HSCT),[m] if eligible**

Refractory disease → **Salvage chemotherapy[n] or Best supportive care** → **HSCT,[m] if eligible**

Extranasal → **Stage I, II, IV**

Stage II, IV

CR or PR → **Consider HSCT[m]**

Refractory disease → **Salvage chemotherapy[n] or Best supportive care**

---

[j]The role of PET scan in this disease is not well established.
[k]See Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[l]Includes a negative ENT evaluation.
[m]Allogeneic preferred, if matched donor available.
[n]Combination chemotherapy regimen (pegaspargase-based), see Suggested Treatment Regimens (NKTL-B).

Adapted with permission from Kohrt H, Lee M, Advani R. Risk stratification in extranodal natural killer/T-cell lymphoma. Expert Rev Anticancer Ther 2010;10:1395-1405.

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Extranodal NK/T-Cell Lymphoma, nasal type

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NK/T-CELL LYMPHOMA PROGNOSTIC INDEX[a]

<u>ALL PATIENTS</u>

Serum LDH > normal
B symptoms
Lymph nodes, N1 to N3, not M1
Ann Arbor Stage IV

	Number of risk factors
Low	0
Low intermediate	1
High intermediate	2
High	3 or 4

[a]Lee J, Suh C, Park YH, et al. Extranodal natural killer T-cell lymphoma, nasal-type: A prognostic model from a retrospective multicenter study. J Clin Oncol 2006;24:612-618.
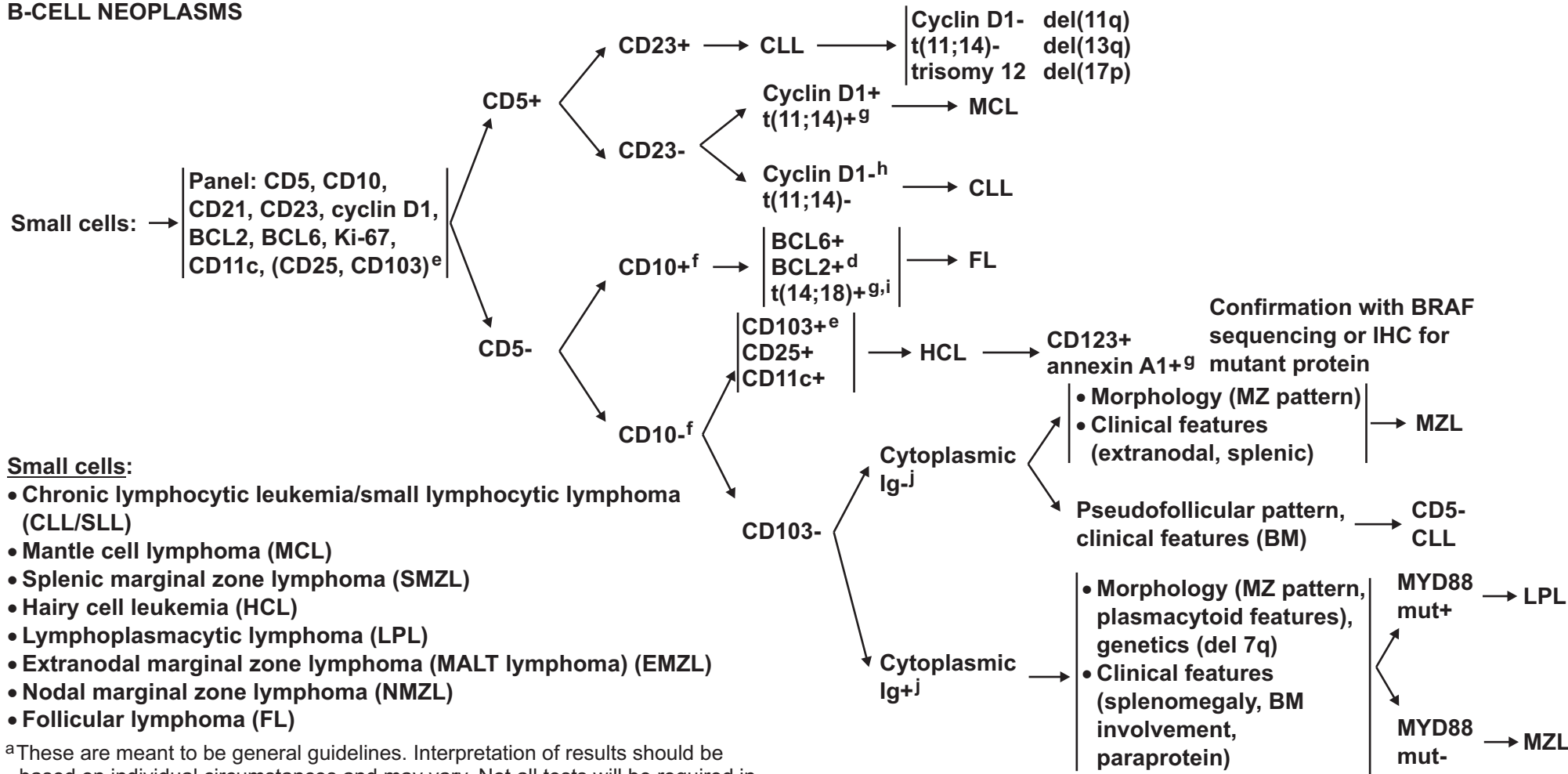
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Extranodal NK/T-Cell Lymphoma, nasal type

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SUGGESTED TREATMENT REGIMENS[a]

(in alphabetical order)

Combination chemotherapy regimen (pegaspargase based)
- AspaMetDex (pegaspargase, methotrexate, and dexamethasone) (Reported as a second-line regimen.)
- SMILE (steroid [dexamethasone], methotrexate, ifosfamide, pegaspargase, and etoposide)

Concurrent chemoradiation therapy (CCRT)
- CCRT (radiation 50 Gy and 3 courses of DeVIC [dexamethasone, etoposide, ifosfamide, and carboplatin])
- CCRT (radiation 40 to 52.8 Gy and cisplatin) followed by 3 cycles of VIPD (etoposide, ifosfamide, cisplatin, and dexamethasone)

Sequential chemoradiation
- SMILE followed by RT 45-50.4 Gy
- VIPD followed by RT 45-50.4 Gy

Radiotherapy alone
- Recommended tumor dose is ≥50 Gy
  ➤ Early or up-front RT had an essential role in improved OS and DFS in patients with localized extranodal NK/T-cell lymphoma, nasal-type, in the upper aerodigestive tract.
  ➤ Up-front RT may yield more benefits on survival in patients with stage I disease.

[a]See references for regimens NKTL-B 2 of 2.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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Extranodal NK/T-Cell Lymphoma, nasal type**

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SUGGESTED TREATMENT REGIMENS

References

Combination Chemotherapy Regimen

Yamaguchi M, Suzuki R, Kwong YL, et al. Phase I study of dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) chemotherapy for advanced-stage, relapsed or refractory extranodal natural killer (NK)/T-cell lymphoma and leukemia. Cancer Sci 2008;99:1016-1020.

Yamaguchi M, Kwong YL, Kim WS, et al. Phase II study of SMILE chemotherapy for newly diagnosed stage IV, relapsed, or refractory extranodal natural killer (NK)/T-cell lymphoma, nasal type: The NK-Cell Tumor Study Group Study. J Clin Oncol 2011;29:4410-4416.

Jaccard A, Gachard N, Marin B, et al. Efficacy of L-asparaginase with methotrexate and dexamethasone (AspaMetDex regimen) in patients with refractory or relapsing extranodal NK/T-cell lymphoma, a phase 2 study. Blood 2011;117:1834-1839.

Concurrent Chemoradiotherapy

Yamaguchi M, Tobinai K, Oguchi M, et al. Concurrent chemoradiotherapy for localized nasal natural killer/T-cell lymphoma: an updated analysis of the Japan clinical oncology group study JCOG0211. J Clin Oncol 2012;30:4044-4046.

Kim SJ, Kim K, Kim BS, et al. Phase II trial of concurrent radiation and weekly cisplatin followed by VIPD chemotherapy in newly diagnosed, stage IE to IIE, nasal, extranodal NK/T-cell lymphoma: Consortium for Improving Survival of Lymphoma study. J Clin Oncol 2009;27:6027-6032. Yamaguchi M, Tobinai K, Oguchi M, et al. Phase I/II study of concurrent chemoradiotherapy for localized nasal natural killer/T-cell lymphoma: Japan Clinical Oncology Group Study JCOG0211. J Clin Oncol 2009;27:5594-5600.

Radiotherapy Alone

Huang MJ, Jiang Y, Liu WP, et al. Early or up-front radiotherapy improved survival of localized extranodal NK/T-cell lymphoma, nasal-type in the upper aerodigestive tract. Int J Radiat Oncol Biol Phys 2008;70:166-174.

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NKTL-B
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DIAGNOSIS

ESSENTIAL:
- **Histopathology and adequate immunophenotype to establish diagnosis. Rebiopsy if consult material is nondiagnostic.**
  - ➤ **IHC panel: CD3, CD5, CD10, BCL6, BCL2, IRF4/MUM1, CD20, CD79a, PAX5, Ki-67, kappa, lambda**
  - ➤ **Cell surface marker analysis by flow cytometry: CD3, CD5, CD7, CD4, CD8, CD19, CD20, CD10, Kappa, lambda**
- **Epstein-Barr virus evaluation by EBV-LMP1 or EBER-ISH (if EBV-LMP1 negative, EBER-ISH is recommended)**

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- **Additional immunophenotyping**
  - ➤ **IHC panel: CD15, CD30, CD45, CD7, CD4, CD8, ALK, TIA-1, Granzyme B, CD57, CD56, CD138**
  - ➤ **Cell surface marker analysis by flow cytometry: CD138, cytoplasmic Kappa and lambda, CD30, CD57, CD56, CD16, CD25, CD52.**
- **Molecular analysis to detect: IgH gene rearrangements**
- ***BCL6* gene mutation analysis[a]**
- **EBV by southern blot**

WORKUP

ESSENTIAL:
- **Performance status**
- **Albumin**
- **Immunosuppressive regimen**
- **LDH, electrolytes, BUN, creatinine**
- **CBC, differential**
- **Hepatitis B testing[b]**
- **Chest/abdomen/pelvis CT**

USEFUL IN SELECTED CASES:
- **MUGA scan/echocardiogram if treatment includes regimens containing anthracyclines or anthracenediones**
- **Bone marrow evaluation**
- **PET-CT scan**
- **Brain MRI**
- **EBV PCR**
- **CMV PCR**
- **EBV serology for primary versus reactivation**

Early lesions ⟶

Polymorphic ⟶ → **See First-line Therapy (PTLD-2)**

Monomorphic ⟶

Classic Hodgkin lymphoma ⟶ **See NCCN Guidelines for Hodgkin Lymphoma**

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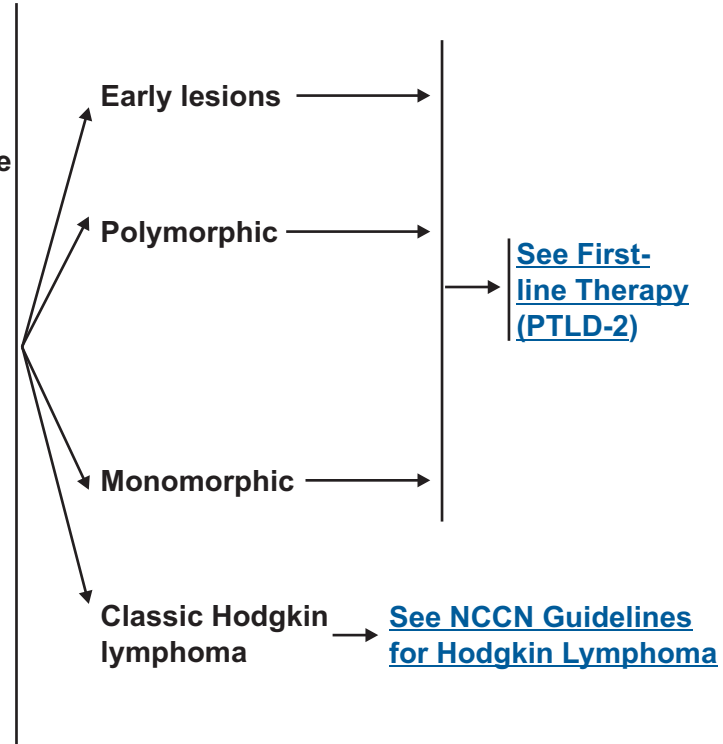
[a] *BCL6* positivity has been associated with a poor response to reduction in immunosuppressive therapy.

[b] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

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PTLD SUBTYPE	FIRST-LINE THERAPY	INITIAL RESPONSE	SECOND-LINE THERAPY

Early lesions → **Reduction of immunosuppressive (RI)[d]**

- **Complete response** → Manage immunosuppression[g] and monitor EBV PCR
- **Persistent or progressive disease** → Rituximab and monitor EBV PCR

Polymorphic

Systemic
- RI, if possible[d] and:
  ➤ Rituximab alone
  or
  ➤ Chemoimmunotherapy[e]

Localized
- RI, if possible[d] and:
  ➤ RT ± rituximab
  or
  ➤ Surgery ± rituximab
  or
  ➤ Rituximab alone

- **Complete response** → • Monitor EBV PCR and:
  ➤ Observation
  or
  ➤ Continue RI, if possible ± maintenance rituximab
- **Persistent or progressive disease** → Chemoimmunotherapy[e] or Clinical trial or EBV-specific cytotoxic T-cell immunity (if EBV driven)

Monomorphic[c]
- RI, if possible[d] and/or:
  ➤ Rituximab alone[f]
  or
  ➤ Chemoimmunotherapy[e]

- **Complete response** → See appropriate histology guidelines for follow-up
- **Persistent or progressive disease** → If RI was initial therapy, then rituximab or chemoimmunotherapy[e] or If rituximab monotherapy was initial therapy, then chemoimmunotherapy[e] or Clinical trial or EBV specific cytotoxic T-cell immunity (if EBV-driven)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

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[c] Treatment is based on the unique histology.

[d] Response to RI therapy is variable and patients need to be closely monitored; RI should be coordinated with the transplant team.

[e] Concurrent or sequential chemoimmunotherapy, See Suggested Treatment Regimens (PTLD-A).

[f] As part of a step-wise approach in patients who are not highly symptomatic or cannot tolerate chemotherapy secondary to comorbidity.

[g] Re-escalation of immunosuppressive should be individualized, taking into account the extent of initial RI and the nature of the organ allograft. These decisions should be made in conjunction with the transplant team.


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SUGGESTED TREATMENT REGIMENS
(in alphabetical order)

Concurrent chemoimmunotherapy
- RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)
- RCHOEP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, etoposide)[a]
- For frail patients who cannot tolerate anthracycline, no specific regimen has been identified but options may include:
  - ‣ RCVP (rituximab, cyclophosphamide, vincristine, prednisone)[a]
  - ‣ RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine)[a]
  - ‣ RCEOP (rituximab, cyclophosphamide, etoposide, vincristine, prednisone)[a]

Sequential chemoimmunotherapy
- Rituximab 375 mg/m^2 weekly x 4 weeks followed by CHOP-21 ± rituximab starting Day 1 of week 9 x 4 cycles

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Consider prophylaxis for tumor lysis syndrome (**See NHODG-B**)

See monoclonal antibody and viral reactivation (**NHODG-B**)

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[a] There are no published data regarding the use of these regimens; however, they are used at NCCN Member Institutions for the treatment of PTLD.

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T-Cell Prolymphocytic Leukemia

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DIAGNOSIS

ESSENTIAL:
- Tissue histology not essential for diagnosis
- Peripheral blood smear analysis for morphology
- Peripheral blood flow cytometry to establish diagnosis[a]
  - ▸ TdT, CD 1a, CD2, CD3, CD4, CD5, CD7, CD8, CD52, TCRαβ
- Cytogenetics: inv(14)(q11;q32); t(14;14)(q11;q32); t(X;14)(q28;q11); trisomy 8

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- Molecular analysis to detect: TCRβ, TCRγ gene rearrangement; *MTCP1* gene rearrangement; *ATM* mutation; *TCL1* overexpression
- Bone marrow biopsy
  - ▸ IHC panel: CD1a, TdT, CD2, CD3, CD5, TCL1

WORKUP

ESSENTIAL:
- Complete H&P examination, including complete skin exam, and evaluation of lymph nodes, spleen, and liver.
- Performance status
- LDH, electrolytes, BUN, creatinine
- CBC, differential
- Chest/abdomen/pelvis CT

USEFUL IN SELECTED CASES:
- MUGA scan/echocardiogram if treatment includes regimens containing anthracyclines or anthracenediones
- Bone marrow evaluation
- PET-CT scan
- HTLV-1 serology: ELISA and confirmatory Western blot if ELISA positive
- Consider screening for active infections and CMV serology if therapy with alemtuzumab is contemplated

Asymptomatic[b] → Observe until progression or symptomatic

Symptomatic disease → See TPLL-2

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[a] Typical immunophenotype: CD1a-, TdT-, CD2+, sCD3+/-, cCD3+/-, CD5+, CD7++, CD52++, TCRαβ+, CD4+/CD8- (65%), CD4+/CD8+ (21%), CD4-/CD8+ (13%).

[b] In a minority of patients, the disease may be asymptomatic and can follow an indolent course of variable duration. In these selected cases expectant observation is a reasonable option.

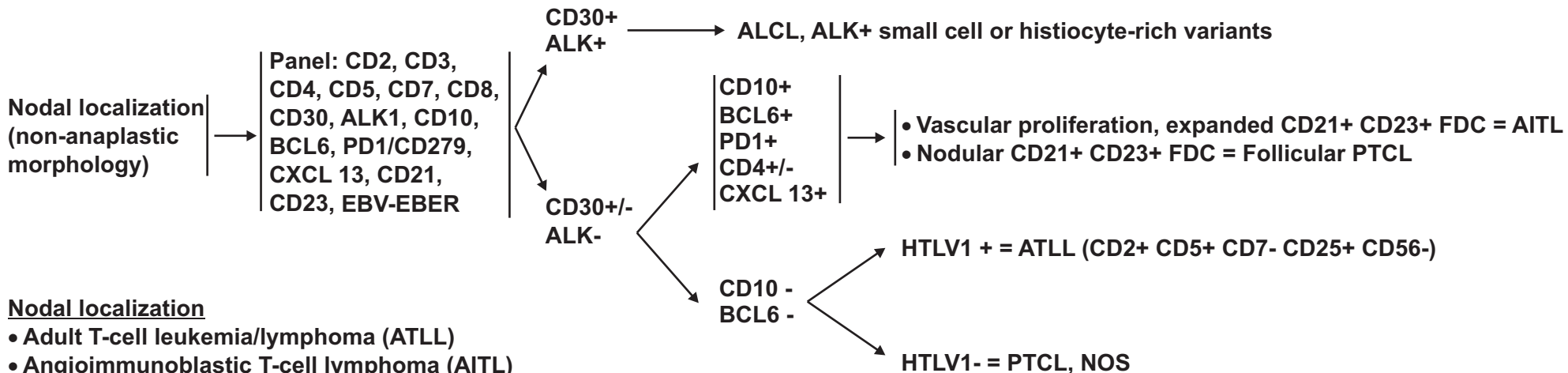**Note:** All recommendations are category 2A unless otherwise indicated.
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T-Cell Prolymphocytic Leukemia

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SYMPTOMATIC DISEASE	PRIMARY TREATMENT[c]	INITIAL RESPONSE	CONSOLIDATION[c]	SALVAGE/ SECOND-LINE THERAPY[c]

Symptomatic disease →

- **Clinical trial (preferred)**
- **Intravenous[d] alemtuzumab alone[e]**
- **Alemtuzumab-containing regimens[e]**
  - ➤ **FMC (fludarabine, mitoxantrone, cyclophosphamide) followed by IV[d] alemtuzumab**
  - ➤ **IV[d] alemtuzumab and pentostatin**

Complete or partial response → **Consider allogeneic stem cell transplant (if donor available)**

No response or progressive disease →

- **Clinical trial (preferred)**
- **Consider alternate regimens not used in primary treatment**

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

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[c] See Treatment References (TPLL-A).

[d] IV alemtuzumab is preferred over subcutaneous based on data showing inferior activity with subcutaneous delivery in patients with T-PLL (Dearden CE, Khot A, Else M, et al. Alemtuzumab therapy in T-cell prolymphocytic leukaemia: Comparing efficacy in a series treated intravenously and a study piloting the subcutaneous route. Blood 2011;118:5799-5802).

[e] Monitor for CMV reactivation; anti-infective prophylaxis for herpes virus and PCP recommended when treating with alemtuzumab ± purine analogs.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

TREATMENT REFERENCES

Alemtuzumab

Dearden CE, Matutes E, Cazin B, et al. High remission rate in T-cell prolymphocytic leukemia with CAMPATH-1H. Blood 2001;98:1721-1726.

Keating MJ, Cazin B, Coutre S, et al. Campath-1H treatment of T-cell prolymphocytic leukemia in patients for whom at least one prior chemotherapy regimen has failed. J Clin Oncol 2002;20:205-213.

Dearden CE, Khot A, Else M, et al. Alemtuzumab therapy in T-cell prolymphocytic leukaemia: Comparing efficacy in a series treated intravenously and a study piloting the subcutaneous route. Blood 2011;118:5799-5802.

Alemtuzumab + pentostatin

Ravandi F, Aribi A, O'Brien S, et al. Phase II study of alemtuzumab in combination with pentostatin in patients with T-cell neoplasms. J Clin Oncol 2009;27:5425-5430.

FMC (fludarabine, mitoxantrone, cyclophosphamide) followed by alemtuzumab

Hopfinger G, Busch R, Pflug N, et al. Sequential chemoimmunotherapy of fludarabine, mitoxantrone, and cyclophosphamide induction followed by alemtuzumab consolidation is effective in T-cell prolymphocytic leukemia. Cancer 2013;119:2258-2267.

Allogeneic stem cell transplant

Castagna L, Nozza A, Bertuzzi A, Siracusano L, Timofeeva I, Santoro A. Allogeneic peripheral blood stem cell transplantation with reduced intensity conditioning in primary refractory prolymphocytic leukemia: graft-versus-leukemia effect without graft-versus-host disease. Bone Marrow Transplant 2001;28:1155-1156.

Kalaycio ME, Kukreja M, Woolfrey AE, et al. Allogeneic hematopoietic cell transplant for prolymphocytic leukemia. Biol Blood Marrow Transplant. 2010;16:543-547.

Murase K, Matsunaga T, Sato T, et al. Allogeneic bone marrow transplantation in a patient with T-prolymphocytic leukemia with small-intestinal involvement. Int J Clin Oncol 2003;8:391-394.

Wiktor-Jedrzejczak W, Dearden C, de Wreede L, et al. Hematopoietic stem cell transplantation in T-prolymphocytic leukemia: A retrospective study from the European Group for Blood and Marrow Transplantation and the Royal Marsden Consortium. Leukemia 2012;26:972-972.

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Hairy Cell Leukemia

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DIAGNOSIS[a]

ESSENTIAL:

- Presence of characteristic hairy cells upon morphologic examination of peripheral blood and characteristic infiltrate with increased reticulin in bone marrow biopsy samples. Dry tap is frequent.
- IHC and flow cytometry are essential for establishing the diagnosis and for distinguishing between hairy cell leukemia and hairy cell variant.[b]
- Adequate immunophenotyping to establish diagnosis[c,d]
  ▸ IHC panel: CD20, CD25, CD123, cyclin D1
    or
  ▸ Cell surface marker analysis by flow cytometry: CD3, CD5, CD10, CD11c, CD19, CD20, CD22, CD25, CD103

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- Molecular analysis to detect: IGHV mutational status
- Sequencing of *BRAF* for V600E mutation or IHC for mutant *BRAF*
- Annexin A1

WORKUP

ESSENTIAL:

- Physical exam: Presence of enlarged spleen and/or liver; presence of peripheral lymphadenopathy (uncommon)
- Performance status
- Peripheral blood examination
- CBC, differential, platelets
- Comprehensive metabolic panel with particular attention to renal function
- LDH
- Bone marrow biopsy ± aspirate
- Hepatitis B testing[e] if rituximab contemplated
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

USEFUL UNDER CERTAIN CIRCUMSTANCES
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Discussion of fertility issues and sperm banking

→ See Initial Treatment (HCL-2)

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[a] This guideline applies to hairy cell leukemia, not hairy cell variant. There are no sufficient data on treatment of hairy cell variant.

[b] Hairy cell variant is characteristically CD25- CD123-, annexin A1-. This helps to distinguish the variant form from classical HCL.

[c] Typical immunophenotype: CD5-, CD10-, CD11c+, CD20+ (bright), CD22+, CD25+, CD103+, CD123+, cyclin D1+, annexin A1+. Monocytopenia is characteristic.

[d] See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).

[e] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

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Hairy Cell Leukemia

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INDICATION FOR TREATMENT

INITIAL TREATMENT[h]

FOLLOW-UP

RELAPSE/ REFRACTORY[h]

- **Systemic symptoms**
- **Splenic discomfort**
- **Recurrent infection**
- **Hemoglobin <12 g/dL**
- **Platelets <100,000/mcL**
- **ANC <1000/mcL**

No indication → **Observe**

Indication present → • **Cladribine**[f] • **Pentostatin**

Complete response[g] → **Observe until indication for treatment**

< Complete response[g]

Relapse at ≥1 year →
- **Retreat with initial purine analog ± rituximab**
- **Alternative purine analog ± rituximab**

Relapse at <1 year

- **Clinical trial**
- **Alternate purine analog ± rituximab**
- **Interferon alpha**
- **Rituximab alone**

> **Consider prophylaxis for tumor lysis syndrome (See NHODG-B)**
>
> **See monoclonal antibody and viral reactivation (NHODG-B)**

Adapted from: Grever MR. How I treat hairy cell leukemia. Blood 2010;115:21-28.

[f]Cladribine should not be administered to patients with active life-threatening or chronic infection.

[g]Complete response defined as: recovery of blood counts (Hgb >12 g/dL, ANC >1500/mcL, platelet >100,000/mcL), absence of HCL cells by morphologic examination of bone marrow biopsy or peripheral blood samples, resolution of organomegaly by physical exam, and absence of disease symptoms. Eradication of minimal residual disease (as determined by flow cytometry, immunohistochemistry, or molecular analysis) is of unproven value at this point.

[h]See Treatment References (HCL-A).

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TREATMENT REFERENCES

Single-agent purine analogs

Flinn IW, Kopecky KJ, Foucar MK, et al. Long-term follow-up of remission duration, mortality, and second malignancies in hairy cell leukemia patients treated with pentostatin. Blood 2000;96:2981-2986.

Goodman GR, Burian C, Koziol JA, Saven A. Extended follow-up of patients with hairy cell leukemia after treatment with cladribine. J Clin Oncol 2003;21:891-896.

Zinzani PL, Tani M, Marchi E, et al. Long-term follow-up of front-line treatment of hairy cell leukemia with 2-chlorodeoxyadenosine. Haematologica 2004;89:309-313.

Chadha P, Rademaker AW, Mendiratta P, et al. Treatment of hairy cell leukemia with 2-chlorodeoxyadenosine (2-CdA): long-term follow-up of the Northwestern University experience. Blood 2005;106:241-246.

Robak T, Jamroziak K, Gora-Tybor J, et al. Cladribine in a weekly versus daily schedule for untreated active hairy cell leukemia: final report from the Polish Adult Leukemia Group (PALG) of a prospective, randomized, multicenter trial. Blood 2007;109:3672-3675.

Else M, Dearden CE, Matutes E, et al. Long-term follow-up of 233 patients with hairy cell leukaemia, treated initially with pentostatin or cladribine, at a median of 16 years from diagnosis. Br J Haematol 2009;145:733-740.

Zenhausern R, Schmitz SF, Solenthaler M, et al. Randomized trial of daily versus weekly administration of 2-chlorodeoxyadenosine in patients with hairy cell leukemia: a multicenter phase III trial (SAKK 32/98). Leuk Lymphoma 2009;50:1501-1511.

Dearden CE, Else M, Catovsky D. Long-term results for pentostatin and cladribine treatment of hairy cell leukemia. Leuk Lymphoma 2011;52 Suppl 2:21-24.

Grever M, Kopecky K, Foucar MK, et al. Randomized comparison of pentostatin versus interferon alfa-2a in previously untreated patients with hairy cell leukemia: an intergroup study. J Clin Oncol 1995;13:974-982.

Tallman MS, Hakimian D, Variakojis D, et al. A single cycle of 2-chlorodeoxyadenosine results in complete remission in the majority of patients with hairy cell leukemia. Blood 1992;80:2203-2209.

Kraut EH, Bouroncle BA, Grever MR. Low-dose deoxycoformycin in the treatment of hairy cell leukemia. Blood 1986;68:1119-1122.

Rituximab

Lauria F, Lenoci M, Annino L, et al. Efficacy of anti-CD20 monoclonal antibodies (Mabthera) in patients with progressed hairy cell leukemia. Haematologica 2001;86:1046-1050.

Nieva J, Bethel K, Saven A. Phase 2 study of rituximab in the treatment of cladribine-failed patients with hairy cell leukemia. Blood 2003;102:810-813.

Thomas DA, O'Brien S, Bueso-Ramos C, et al. Rituximab in relapsed or refractory hairy cell leukemia. Blood 2003;102:3906-3911.

Purine analogs with rituximab

Else M, Osuji N, Forconi F, et al. The role of rituximab in combination with pentostatin or cladribine for the treatment of recurrent/refractory hairy cell leukemia. Cancer 2007;110:2240-2247.

Else M, Dearden CE, Matutes E, et al. Rituximab with pentostatin or cladribine: an effective combination treatment for hairy cell leukemia after disease recurrence. Leuk Lymphoma 2011;52 Suppl 2:75-78.

Ravandi F, O'Brien S, Jorgensen J, et al. Phase 2 study of cladribine followed by rituximab in patients with hairy cell leukemia. Blood 2011;118:3818-3823.

Gerrie AS, Zypchen LN, Connors JM. Fludarabine and rituximab for relapsed or refractory hairy cell leukemia. Blood 2012;119:1988-1991.

Interferon-alpha

Damasio EE, Clavio M, Masoudi B, et al. Alpha-interferon as induction and maintenance therapy in hairy cell leukemia: a long-term follow-up analysis. Eur J Haematol 2000;64:47-52.

Benz R, Siciliano RD, Stussi G, Fehr J. Long-term follow-up of interferon-alpha induction and low-dose maintenance therapy in hairy cell leukemia. Eur J Haematol 2009;82:194-200.

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**NCCN Guidelines Version 4.2014
Non-Hodgkin's Lymphomas**

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USE OF IMMUNOPHENOTYPING/GENETIC TESTING IN DIFFERENTIAL DIAGNOSIS OF MATURE B-CELL AND NK/T-CELL NEOPLASMS[a]
(TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)

GENERAL PRINCIPLES

- Morphology ± clinical features drive both the choice and the interpretation of special studies.
- Differential diagnosis is based on morphology ± clinical setting.
- Begin with a broad but limited panel of antibodies, based on the differential diagnosis.
  - ➤ Avoid "shotgun" panels of unnecessary antibodies unless a clinically urgent situation warrants.
- Add antigens in additional panels, based on initial results.
- Follow with genetic studies as needed.
- Return to clinical picture if immunophenotype + morphology are not specific.

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Non-Hodgkin's Lymphomas

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USE OF IMMUNOPHENOTYPING/GENETIC TESTING IN DIFFERENTIAL DIAGNOSIS OF MATURE B-CELL AND NK/T-CELL NEOPLASMS[a]
(TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)

B-cell antigens positive[b,c] **(CD19, CD20, CD79a, PAX5)**

- **Morphology**
  - **Cytology**
    - **Small cells**
    - **Medium-sized cells**
    - **Large cells**
  - **Pattern**
    - **Diffuse**
    - **Nodular, follicular, mantle, marginal**
    - **Sinuses**
- **Clinical**
  - **Age (child, adult)**
  - **Location**
    - **Nodal**
    - **Extranodal, specific site**
- **Immunophenotype**
  - **Naïve B cells: CD5, CD23**
  - **GCB cells: CD10, BCL6, FDC (CD21, CD23)**
  - **Post-GCB cells: IRF4/MUM1, CD138**
  - **Immunoglobulin heavy and light chains (surface, cytoplasmic, class switch, light chain type)**
  - **Oncogene products: BCL2, cyclin D1, MYC, BCL6, ALK**
  - **Viruses: EBV, HHV8**
  - **Other: CD43, Ki-67**
- **Genetic testing**
  - **BCL2, BCL6, CCND1, MYC, ALK, MYD88, BRAF, IG rearrangement**

T- or NK/T-cell antigens positive[b,c] **(CD2, CD3, CD5, CD7)**
[and B-cell antigens negative]

- **Morphology**
  - **Anaplastic vs. non-anaplastic**
  - **Epidermotropic**
- **Clinical**
  - **Age (child, adult)**
  - **Location**
    - **Cutaneous**
    - **Extranodal noncutaneous (specific site)**
    - **Nodal**
- **Immunophenotype**
  - **CD30, ALK*, CD56, βF1, cytotoxic granule proteins,**
  - **CD4, CD8, CD5, CD7, TCRαβ, TCRγδ, CD1a, TdT**
  - **Follicular T-cells: CD10, BCL6, CD57, CD279 (PD1)**
  - **Viruses: EBV, HTLV1 (clonal)**
- **Genetic testing**
  - **ALK, TCR, HTLV1**

*Always do ALK if CD30+

See Initial Morphologic, Clinical, and Immunophenotypic Analysis
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[a]These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.

[b]Some lymphoid neoplasms may lack pan leukocyte (CD45), pan-B, and pan-T antigens. Selection of additional antibodies should be based on the differential diagnosis generated by morphologic and clinical features (eg, plasma cell myeloma, ALK+ DLBCL, plasmablastic lymphoma, anaplastic large cell lymphoma, NK-cell lymphomas).

[c]Usually 1 Pan-B (CD20) and 1 Pan-T (CD3) markers are done unless a terminally differentiated B-cell or a specific PTCL is suspected.

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(TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)

INITIAL MORPHOLOGIC, CLINICAL, AND IMMUNOPHENOTYPIC ANALYSIS

Lineage-based on immunophenotype[d] (Pan-B and Pan-T antigens) or Suspected by morphology/ clinical features

B-cell neoplasms

Small cells —————————→ **See NHODG-A 4 of 11**

Medium-sized cells —————————→ **See NHODG-A 5 of 11**

Large cells ± anaplastic morphology —————————→ **See NHODG-A 6 of 11**

Cutaneous localization —————————→ **See NHODG-A 8 of 11**

T-cell neoplasms

Anaplastic morphology —————————→ **See NHODG-A 9 of 11**

Cutaneous localization (non-anaplastic morphology) —————————→ **See NHODG-A 10 of 11**

Extranodal, noncutaneous localization (non-anaplastic morphology) —————————→ **See NHODG-A 11 of 11**

Nodal localization (non-anaplastic morphology) —————————→ **See NHODG-A 11 of 11**

[a]These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.
[d]Initial panel will often include additional markers based on morphologic differential diagnosis and clinical features.

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B-CELL NEOPLASMS

Small cells: → Panel: CD5, CD10, CD21, CD23, cyclin D1, BCL2, BCL6, Ki-67, CD11c, (CD25, CD103)[e]

CD5+
- CD23+ → CLL → Cyclin D1-, t(11;14)-, trisomy 12 | del(11q), del(13q), del(17p)
- CD23-
  - Cyclin D1+ t(11;14)+[g] → MCL
  - Cyclin D1-[h] t(11;14)- → CLL

CD5-
- CD10+[f] → BCL6+, BCL2+[d], t(14;18)+[g,i] → FL
- CD10-[f]
  - CD103+[e], CD25+, CD11c+ → HCL → CD123+ annexin A1+[g] → Confirmation with BRAF sequencing or IHC for mutant protein
  - CD103-
    - Cytoplasmic Ig-[j]
      - • Morphology (MZ pattern), • Clinical features (extranodal, splenic) → MZL
      - Pseudofollicular pattern, clinical features (BM) → CD5- CLL
    - Cytoplasmic Ig+[j]
      - • Morphology (MZ pattern, plasmacytoid features), genetics (del 7q), • Clinical features (splenomegaly, BM involvement, paraprotein)
        - MYD88 mut+ → LPL
        - MYD88 mut- → MZL

Small cells:
- Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)
- Mantle cell lymphoma (MCL)
- Splenic marginal zone lymphoma (SMZL)
- Hairy cell leukemia (HCL)
- Lymphoplasmacytic lymphoma (LPL)
- Extranodal marginal zone lymphoma (MALT lymphoma) (EMZL)
- Nodal marginal zone lymphoma (NMZL)
- Follicular lymphoma (FL)

[a] These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.

[e] Flow cytometry on blood or bone marrow done only if HCL is in differential diagnosis by morphology.

[f] Rare cases of HCL may be CD10+ or CD5+ and some cases of FL are CD10-. BCL6 is a useful discriminate if needed (rarely). Rare cases of MCL are CD5-.

[g] Can be done to confirm if necessary.

[h] Rare cases of cyclin D1 and t(11;14) negative MCL have been reported. This diagnosis should be made with extreme caution and with expert consultation.

[i] 85% of follicular lymphoma will be BCL2+ or t(14;18)+.

[j] Kappa and lambda light chains; IgG, IgM, and IgA may be helpful.

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(TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)

B-CELL NEOPLASMS

Diffuse pattern Medium cells ± starry sky pattern[k] → Initial Panel: CD5, CD10, cyclin D1, BCL2, BCL6, Ki-67[l]

CD5+
- Cyclin D1+ → MCL,[m] blastoid variant
- Cyclin D1- BCL6+/- IRF4/MUM1+/- →
  - CLL with increased prolymphocytes
  - DLBCL, NOS CD5+
  - If BCL6- MUM1-, consider cyclin D1- MCL

CD5-

CD10+
- BCL6+ BCL2- → FISH for *MYC, BCL2, BCL6* →
  - *MYC+ BCL2- BCL6-* → BL[n]
  - *MYC+/- BCL2+ BCL6+/-* → U-DLBCL/BL
- BCL6+ BCL2+ → U-DLBCL/BL → FISH for *MYC, BCL2, BCL6* to check for "double hit"
- BCL6- → Consider plasma cell neoplasm

CD10-
- BCL6+ BCL2- IRF4/MUM1- → FISH for *MYC, BCL2, BCL6* →
  - *MYC+ BCL2- BCL6-* → BL?
  - *MYC+/- BCL2+ BCL6+/-* → U-DLBCL/BL
- BCL6+/- BCL2+ IRF4/MUM1+/- → U-DLBCL/BL → FISH for *MYC, BCL2, BCL6* to check for "double hit"

Medium cells
- Burkitt lymphoma (BL)
- Diffuse large B-cell lymphoma (DLBCL)
- Mantle cell lymphoma (MCL), blastoid variant
- B-cell lymphoma (BCL), unclassifiable, intermediate between DLBCL and BL (U-DLBCL/BL)

[a]These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.

[k]Starry sky pattern is typically present in BL and frequently in U-DLBCL/BL.

[l]Ki-67 is a prognostic factor in some lymphomas. (eg, mantle cell and is typically >90% in Burkitt lymphoma.) It is not useful in predicting the presence of MYC rearrangement or in classification.

[m]Rare MCL may be cyclin D1-.

[n]Rare BL may lack detectable MYC rearrangement. Correlation with morphology and clinical features is essential.

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(TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)

B-CELL NEOPLASMS

Large cells: → Panel:[o] CD5, CD10, BCL6, IRF4/MUM1, Ki-67[l]

- CD5+
  - Cyclin D1+ → Pleomorphic MCL
  - Cyclin D1- → DLBCL, NOS CD5+
- CD5- → DLBCL
  - CD10+ → DLBCL, NOS GCB type (BCL6+)
  - CD10-
    - BCL6+ IRF4/MUM1- → DLBCL, NOS GCB type
    - BCL6+ IRF4/MUM1+ → Non-GCB
    - BCL6- IRF4/MUM1+ → Post-GCB

GCB= Germinal center B-cell like

Panel: CD20, PAX5, CD138, ALK1, CD30, CD15, EBV-EBER, HHV8, Ig light and heavy chains (If further characterization is warranted based on clinical or morphologic features. The specific panel will vary depending on the differential diagnosis.) →
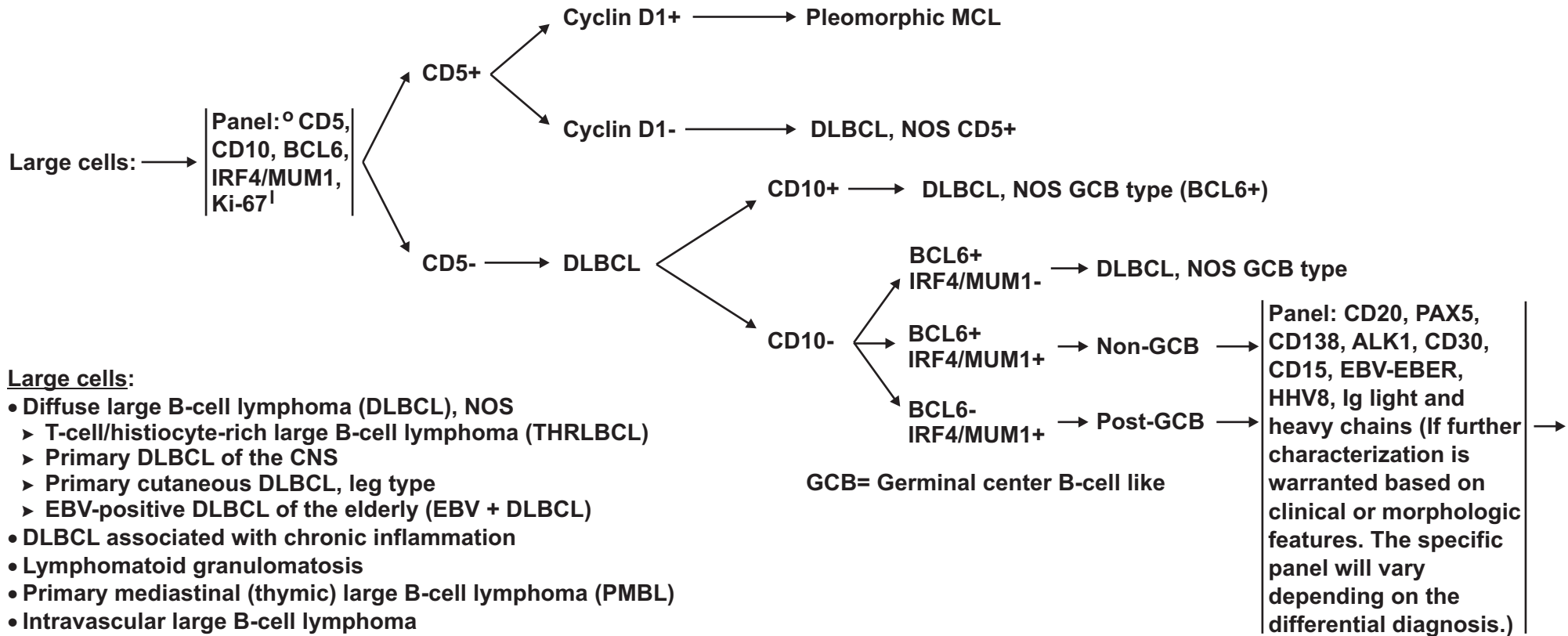
Large cells:
- Diffuse large B-cell lymphoma (DLBCL), NOS
  - ‣ T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL)
  - ‣ Primary DLBCL of the CNS
  - ‣ Primary cutaneous DLBCL, leg type
  - ‣ EBV-positive DLBCL of the elderly (EBV + DLBCL)
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma (PMBL)
- Intravascular large B-cell lymphoma
- ALK-positive large B-cell lymphoma
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease (LBCL in HHV8 + MCD)
- Primary effusion lymphoma
- B-cell lymphoma, unclassifiable, intermediate between DLBCL (U-DLBCL) and classical Hodgkin lymphoma (CHL)
- Mantle cell lymphoma (MCL), pleomorphic variant

[a] These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.

[l] Ki-67 is a prognostic factor in some lymphomas. (eg, mantle cell and is typically >90% in Burkitt lymphoma.) It is not useful in predicting the presence of MYC rearrangement or in classification.

[o] CD5 is included to identify pleomorphic MCL; if CD5 is positive, cyclin D1 staining is done to confirm or exclude MCL.

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Large cells (continued)

CD20+ (PAX5+)

- **EBER-**
  - **CD30 -**
    - T-cell-rich → THRLBCL (May be BCL6+, IRF4/MUM1-)
    - DLBCL, non-GCB
  - **CD30 +**
    - Mediastinal → PMBL (May be BCL6+, IRF4/MUM1-)
    - Morphologically borderline with CHL
      - CD15- → PMBL
      - CD15+ → U-DLBCL/CHL
- **EBER+**
  - Elderly or immunosuppressed → EBV + DLBCL
  - Extranodal, T-cell rich, angiocentric → Lymphomatoid granulomatosis
  - Chronic inflammation → DLBCL associated with chronic inflammation
- **EBER- HHV8+** → LBCL in HHV8 + MCD (IgM lambda +) confirm by morphology

CD20- (PAX5-) CD79a+ MUM1+

- **CD138+/-**
  - **EBV+/- HHV8-** → Plasmablastic lymphoma → *MYC* FISH +
  - **EBV+/- HHV8+** → PEL (CD30+)
  - **EBV- ALK+** → ALK + DLBCL → IgA lambda + EMA +
  - **EBV- ALK- HHV8-** → Anaplastic/Plasmablastic myeloma/plasmacytoma → CD56 +/- Cyclin D1 +/- IgG, IgA, kappa, or lambda

[a]These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.

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(TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)

B-CELL NEOPLASMS

FDC = Follicular dendritic cells

Cutaneous localization →

Panel: CD3, CD5, CD10,[p] BCL2, BCL6,[p] IRF4/MUM1, CD21/23 (FDC markers)

CD10+ → PCFCL

CD10-

BCL2-
- BCL6+ / IRF4/MUM1- / (FDC+/-) / Small/medium/large cells / Many CD3+ cells → PCFCL
- BCL6- (positive GC) / IRF4/MUM1+/- / (FDC + follicular, disrupted) / Small/medium cells / (Larger cells in GC) → PCMZL

BCL2+
- BCL2 strongly + / BCL6+/- / IRF4/MUM1+ / (FDC -) / Large round cells / Few CD3+ T-cells → PC-DLBCL, leg type
- BCL6- (positive GC) / IRF4/MUM1+/- / (FDC + follicular, disrupted) / Small/medium cells → PCMZL
- BCL2 weakly + / BCL6+ / IRF4/MUM1- / (FDC±, follicular) / Small/medium/large cells / Many CD3+ T-cells → PCFCL

- **Primary cutaneous marginal zone lymphoma (PCMZL)**
- **Primary cutaneous follicle center lymphoma (PCFCL)**
- **Primary cutaneous DLBCL, leg type (PC-DLBCL, leg type)**

[a] These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.

[p] These are assessed both in follicles (if present) and in intrafollicular/diffuse areas. CD10+ BCL6 + germinal centers are present in PCMZL, while both follicular and interfollicular/diffuse areas (tumor cells) are positive for BCL6+/- CD10 in PCFCL.

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(TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)

T-CELL NEOPLASMS

Diagnostic algorithm:

Anaplastic morphology → **Panel: CD30, CD15, PAX5,[q] ALK, EBV-EBER, cytotoxic granule proteins (granzyme B, perforin, TIA1), CD25, MUM1**

- **CD30+ strong, all cells**
  - **ALK+** → **ALCL, ALK+**
  - **ALK-**
    - **PAX5+**
      - If only one T-cell antigen expressed, could be DLBCL
      - **PAX5 Dim+ CD15+ EBER+/-** → Consider CHL (T-cell antigen expression may rarely occur in CHL)
    - **PAX5-** →
      - Cutaneous = Primary cutaneous CD30+ T-cell LPD
        - ▸ Polymorphous, regressing = LyP
        - ▸ Monomorphous, progressing = PC-ALCL
        - ▸ MF in transformation (if history of MF)
      - Non-cutaneous = ALCL, ALK- (caveat: rule out nodal involvement by CTCL, CD15 maybe + in CTCL)
      - Intestinal = EATL (eosinophils: clinical history of celiac disease or antibodies)
      - HTLV1+ = ATLL, anaplastic large cell type (CD25+)
- **CD30 or focal** → **PTCL-NOS**

Anaplastic morphology
- Anaplastic large cell lymphoma (ALCL), ALK positive
- Anaplastic large cell lymphoma (ALCL), ALK negative
- Adult T-cell leukemia/lymphoma (ATLL), anaplastic large cell type
- Enteropathy associated T-cell lymphoma (EATL)
- Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
  - ▸ Lymphomatoid papulosis (LyP)
  - ▸ Primary cutaneous anaplastic large cell lymphoma (PC-ALCL)

[a] These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.

[q] Rare T-cell lymphomas may be CD20+ or PAX5+. Assessment of other Pan-T and -B markers is essential. The expression of multiple markers of 1 lineage and only 1 of the other lineages supports lineage assignment. PCR analysis may be required to determine lineage in such cases.

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T-CELL NEOPLASMS
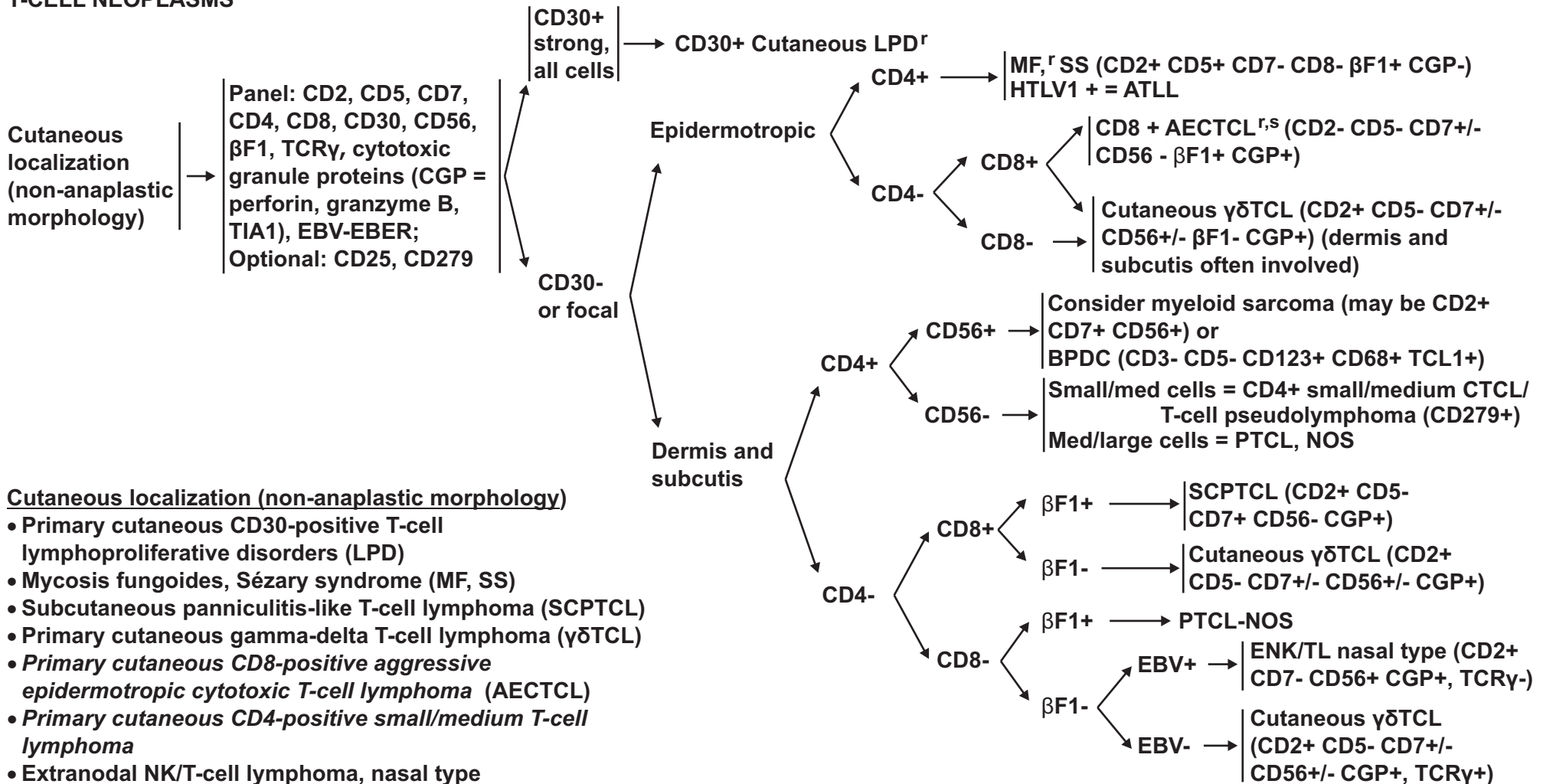
Cutaneous localization (non-anaplastic morphology)
- Primary cutaneous CD30-positive T-cell lymphoproliferative disorders (LPD)
- Mycosis fungoides, Sézary syndrome (MF, SS)
- Subcutaneous panniculitis-like T-cell lymphoma (SCPTCL)
- Primary cutaneous gamma-delta T-cell lymphoma (γδTCL)
- *Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma* (AECTCL)
- *Primary cutaneous CD4-positive small/medium T-cell lymphoma*
- Extranodal NK/T-cell lymphoma, nasal type
- Peripheral T-cell lymphoma, NOS
- Blastic plasmacytoid dendritic cell (BPDC) neoplasm

[a] These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.
[r] A minority of MF cases can be CD30+, CD4-, and CD8+/-, TIA1+. ATLL may also be CD30+.
[s] AECTCL has distinctive morphology and clinical presentation.

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(TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)

Extranodal, noncutaneous localization (non-anaplastic morphology) →

Panel: CD2, CD3, CD4, CD5, CD7, CD8, CD30, CD56, ALK1, βF1, TCRγ, MUM1, cytotoxic granule proteins (CGP = perforin, granzyme B, TIA1), EBV-EBER

EBER+ → ENKTCL (CD5- CD4- CD8- CD30- CD56+ CGP+, midline face, upper aerodigestive tract, testis, GI tract) (may have T-cell phenotype)

EBER-
- **CD30+**
  - **ALK+** → ALCL, ALK+ small cell or histiocyte-rich variants
  - **ALK-** →
    - Intestinal, other abdominal/visceral sites, celiac disease or markers positive = EATL Type 1 (CD5- CD7- CD4- CD8+/- CD56+/- TIA1+ GRB+ Perf+)
    - Other sites, celiac disease markers negative = PTCL, NOS (usually less strongly CD30+)
- **CD30-** →
  - Intestine, epidermorphic = EATL Type 2
  - Liver, spleen, bone marrow sinuses, immune suppression = HSTCL (CD5- CD7- CD4- CD8- CD56+ TIA1+ GRB- Perf-)
  - Other sites = PTCL, NOS

Extranodal, noncutaneous localization
- Extranodal NK/T cell lymphoma, nasal type (ENKTCL)
- Enteropathy-associated T-cell lymphoma (EATL)
- Hepatosplenic T-cell lymphoma (HSTCL)
- Peripheral T-cell lymphoma, NOS (PTCL, NOS)
- ALCL, ALK+ small cell and histiocyte-rich variants

Nodal localization (non-anaplastic morphology) →

Panel: CD2, CD3, CD4, CD5, CD7, CD8, CD30, ALK1, CD10, BCL6, PD1/CD279, CXCL 13, CD21, CD23, EBV-EBER

CD30+ ALK+ → ALCL, ALK+ small cell or histiocyte-rich variants

CD30+/- ALK-
- **CD10+ BCL6+ PD1+ CD4+/- CXCL 13+** →
  - Vascular proliferation, expanded CD21+ CD23+ FDC = AITL
  - Nodular CD21+ CD23+ FDC = Follicular PTCL
- **CD10 - BCL6 -**
  - HTLV1 + = ATLL (CD2+ CD5+ CD7- CD25+ CD56-)
  - HTLV1- = PTCL, NOS

Nodal localization
- Adult T-cell leukemia/lymphoma (ATLL)
- Angioimmunoblastic T-cell lymphoma (AITL)
- Peripheral T-cell lymphoma, NOS (PTCL, NOS)
- ALCL, ALK+ small cell and histiocyte-rich variants

[a]These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.

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SUPPORTIVE CARE FOR NHL

Tumor Lysis Syndrome (TLS)

- **Laboratory hallmarks of TLS:**
  - ► **High potassium**
  - ► **High uric acid**
  - ► **High phosphorous**
  - ► **Low calcium**

- **Symptoms of TLS:**
  - ► **Nausea and vomiting, shortness of breath, irregular heartbeat, clouding of urine, lethargy, and/or joint discomfort.**

- **High-risk features**
  - ► **Histologies of Burkitt Lymphoma and Lymphoblastic Lymphoma; occasionally patients with DLBCL and CLL**
  - ► **Spontaneous TLS**
  - ► **Elevated WBC**
  - ► **Bone marrow involvement**
  - ► **Pre-existing elevated uric acid**
  - ► **Ineffectiveness of allopurinol**
  - ► **Renal disease or renal involvement by tumor**

- **Treatment of TLS:**
  - ► **TLS is best managed if anticipated and treatment started prior to chemotherapy.**
  - ► **Centerpiece of treatment includes**
    - ◊ **Rigorous hydration**
    - ◊ **Management of hyperuricemia**
    - ◊ **Frequent monitoring of electrolytes and aggressive correction is essential**
  - ► **First-line and at retreatment**
    - ◊ **Allopurinol beginning 2-3 days prior to chemotherapy and continued for 10-14 days**
      or
      Rasburicase is indicated for patients with any of the following risk factors:
        - **- presence of any high-risk feature**
        - **- urgent need to initiate therapy in a high-bulk patient**
        - **- situations where adequate hydration may be difficult or impossible**
        - **- Acute renal failure**
    - ◊ **One dose of rasburicase is frequently adequate. Doses of 3-6 mg are usually effective. Redosing should be individualized.**
  - ► **If TLS is untreated, its progression may cause acute kidney failure, cardiac arrhythmias, seizures, loss of muscle control, and death.**

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SUPPORTIVE CARE FOR NHL

Monoclonal Antibody Therapy and Viral Reactivation

Anti-CD20 Antibody Therapy

Hepatitis B virus (HBV):
- Hepatitis B surface antigen (HBsAg) and Hepatitis B core antibody (HBcAb) testing for all patients receiving anti-CD20 antibody therapy
  - ► Quantitative hepatitis B viral load by PCR only if one of the screening tests is positive
  - ► In areas with high prevalence/population or prevalence of HBV is not known, recommend testing all patients receiving immunotherapy, chemotherapy, or chemoimmunotherapy
- Note: Patients receiving IV immunoglobulin (IVIG) may be HBcAb-positive as a consequence of IVIG therapy.
- Prophylactic antiviral therapy with entecavir is recommended for any patient who is HBsAg-positive and receiving anti-lymphoma therapy. In cases of HBcAb positivity, prophylactic antiviral therapy is preferred; however, if there is a concurrent high-level hepatitis B surface antibody, these patients may be monitored with serial hepatitis B viral load.
  - ► Entecavir is preferred based on Huang YH, et al. J Clin Oncol 2013;31:2765-2772; Huang H, et al. J Clin Oncol 2013;31:Abstract 8503
  - ► Avoid lamivudine due to risks of resistance development.
  - ► Monitor hepatitis B viral load with PCR monthly through treatment and every 3 months thereafter
    - ◊ If viral load is consistently undetectable, treatment is considered prophylactic
    - ◊ If viral load fails to drop or previously undetectable PCR becomes positive, consult hepatologist and discontinue anti-CD20 antibody therapy
  - ► Maintain prophylaxis up to 12 mo after oncologic treatment ends
    - ◊ Consult with hepatologist for duration of therapy in patient with active HBV

Hepatitis C virus (HCV):
- New evidence from large epidemiology studies, molecular biology research, and clinical observation supports an association of HCV and B-cell NHL. Recently approved direct-acting antiviral agents (DAA) for chronic carriers of HCV with genotype 1 demonstrated a high rate of sustained viral responses.
  - ► Low-grade B-cell NHL
    - ◊ According to the American Association for the Study of Liver Diseases, combined therapy with DAA should be considered in asymptomatic patients with HCV genotype 1 since this therapy can result in regression of lymphoma.
  - ► Aggressive B-cell NHL
    - ◊ Patients should be initially treated with chemoimmunotherapy regimens according to NCCN Guidelines for NHL.
    - ◊ Liver functional tests and serum HCV RNA levels should be closely monitored during and after chemoimmunotherapy for development of hepatotoxicity.
    - ◊ Antiviral therapy should be considered in patients in complete remission after completion of lymphoma therapy.

Anti-CD20 Antibody Therapy and Brentuximab Vedotin

Progressive multifocal leukoencephalopathy (PML):
- Caused by the JC virus and is usually fatal.
  - ► Diagnosis made by PCR of CSF and in some cases brain biopsy.
- No known effective treatment.
- Clinical indications may include changes in behavior such as confusion, dizziness or loss of balance, difficulty talking or walking, and vision problems.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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SUPPORTIVE CARE FOR NHL

Monoclonal Antibody Therapy and Viral Reactivation (continued)

Anti-CD52 Antibody Therapy: Alemtuzumab

Cytomegalovirus (CMV) reactivation:

- The current appropriate management is controversial; some NCCN Member Institutions use ganciclovir (oral or IV) preemptively if viremia is present, others only if viral load is rising.
- CMV viremia should be measured by quantitative PCR at least every 2-3 wks.
- Consultation with an infectious disease expert may be necessary. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

Rituximab Rapid Infusion

- If no infusion reactions were experienced with prior cycle of rituximab, a rapid infusion over 90 min can be used.

Methotrexate and Glucarpidase

- Consider use of glucarpidase if significant renal dysfunction and methotrexate levels are >10 microM beyond 42-48 h. Leucovorin remains a component in the treatment of methotrexate toxicity and should be continued for at least 2 days following glucarpidase administration. However, be aware that leucovorin is a substrate for glucarpidase, and therefore should not be administered within two hours prior to or following glucarpidase.

Note: All recommendations are category 2A unless otherwise indicated.
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RESPONSE CRITERIA FOR NON-HODGKIN'S LYMPHOMA
(not including PET)

Response Category	Physical Examination	Lymph Nodes	Lymph Node Masses	Bone Marrow
CR	Normal	Normal	Normal	Normal
CRu (unconfirmed)	Normal	Normal	Normal	Indeterminate
	Normal	Normal	>75% decrease	Normal or indeterminate
PR	Normal	Normal	Normal	Positive
	Normal	≥50% decrease	≥50% decrease	Irrelevant
	Decrease in liver/spleen	≥50% decrease	≥50% decrease	Irrelevant
Relapse/ Progression	Enlarging liver/spleen, new sites	New or increased	New or increased	Reappearance

Source: Table 2 from Cheson BD, Horning SJ, Coiffier B, et al: Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma. J Clin Oncol 1999; 17:1244. Reprinted with permission from the American Society of Clinical Oncology.

See Response Designations and
PET Findings (NHODG-C 2 of 2)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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REVISED RESPONSE CRITERIA FOR NON-HODGKIN'S LYMPHOMA
(including PET)[a]

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥50% of previously involved sites from nadir	Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node >1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	>50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Source: Table 2 from Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25(5):579-586. Reprinted with permission from the American Society of Clinical Oncology.

[a]Recommended for use with Diffuse Large B-Cell Lymphoma and Hodgkin Disease/Lymphoma.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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PRINCIPLES OF RADIATION THERAPY[a]

Field:
- Treatment with photons, electrons, or protons may all be appropriate, depending upon clinical circumstances.
- **Involved-site radiation therapy (ISRT) for nodal sites**
  - ISRT is recommended as the appropriate field for NHL. Planning for ISRT requires modern CT-based simulation and planning capabilities. Incorporating other modern imaging like PET and MRI often enhances field determination.
  - ISRT targets the site of the originally involved lymph node(s). The field encompasses the original suspicious volume prior to chemotherapy or surgery. Yet, it spares adjacent uninvolved organs (like lungs, bone, muscle, or kidney) when lymphadenopathy regresses following chemotherapy.
  - The pre-chemotherapy or pre-biopsy gross tumor volume (GTV) provides the basis for determining the clinical target volume (CTV). Concerns for questionable subclinical disease and uncertainties in original imaging accuracy or localization may lead to expansion of the CTV and are determined individually using clinical judgment. Possible movement of the target by respiration as determined by 4D-CT or fluoroscopy (internal target volume- ITV) should also influence the final CTV.
  - The planning treatment volume (PTV) is an additional expansion of the CTV that accounts only for setup variations (see ICRU definitions).
  - Organs at risk (OAR) should be outlined for optimizing treatment plan decisions.
  - The treatment plan is designed using conventional, 3-D conformal, or IMRT techniques using clinical treatment planning considerations of coverage and dose reductions for OAR.
- **ISRT for extranodal disease**
  - Similar principles as for ISRT nodal sites (see above).
  - For most organs and particularly for indolent disease, the whole organ alone is the CTV (eg, stomach, salivary gland, orbit, thyroid, breast, testis).
  - For bone/spine, localized skin, only the involved part of the organ is irradiated with adequate margins.
  - For most NHL subtypes no radiation is required for uninvolved lymph nodes.

General Dose Guidelines:
- **Localized CLL/SLL: 24-30 Gy**
- **Follicular lymphoma: 24-30 Gy**
- **Marginal zone lymphoma:**
  - Gastric: 30 Gy
  - Other extranodal sites: 24-30 Gy
  - Nodal MZL: 24-30 Gy
- **Early-stage mantle cell lymphoma: 30-36 Gy**
- **Mini-dose RT (2 Gy x 2 may be repeated) for palliation/local control of SLL, FL, MZL, MCL**

- **Diffuse large cell lymphoma or PTCL**
  - Consolidation after chemotherapy CR: 30-36 Gy
  - Complimentary after PR: 40-50 Gy
  - RT as primary treatment for refractory or noncandidates for chemotherapy: 45-55 Gy
  - Salvage pre- or post-stem cell transplantation: 30-40 Gy
- **Primary cutaneous anaplastic large cell lymphoma: 30-36 Gy**

[a]See references on NHODG-D 2 of 2.

Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF RADIATION THERAPY[a]

REFERENCES

Horning SJ, Weller E, Kim K, et al. Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-Hodgkin's lymphoma: Eastern Cooperative Oncology Group study 1484. J Clin Oncol 2004;22:3032-3038.

Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med 1998;339:21-26.

Haas RL, Poortmans P, de Jong D, et al. High response rates and lasting remissions after low-dose involved field radiotherapy in indolent lymphomas, J Clin Oncol 2003;21: 2474-2480.

Campbell BA, Voss N, Woods R, et al. Long-term outcomes for patients with limited stage follicular lymphoma: involved regional radiotherapy versus involved node radiotherapy. Cancer 2010;116:3797-3806.

Lowry L, Smith P, Qian W, et al. Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: a randomised phase III trial. Radiother Oncol 2011;100:86-92.

Goda JS, Gospodarowicz M, Pintilie M, et al. Long-term outcome in localized extranodal mucosa-associated lymphoid tissue lymphomas treated with radiotherapy Cancer 2010;116:3815-3824.

Phan J, Mazloom A, Medeiros LJ, et al: The benefit of consolidative radiation therapy in patients with diffuse large B-cell lymphoma treated with R-CHOP chemotherapy. J Clin Oncol 2010;28:4170-4176.

Campbell BA, Connors JM, Gascoyne RD, et al. Limited-stage diffuse large B-cell lymphoma treated with abbreviated systemic therapy and consolidation radiotherapy: involved-field versus involved-node radiotherapy. Cancer 2012;118:4156-4165.

Note: All recommendations are category 2A unless otherwise indicated.
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SPECIAL CONSIDERATIONS FOR THE USE OF B-CELL RECEPTOR INHIBITORS (IBRUTINIB AND IDELALISIB)[1,2,3]

IBRUTINIB

- **Dosage**
  - ➤ **CLL:** The recommended dose of ibrutinib is 420 mg PO daily, continuous
  - ➤ **MCL:** The recommended dose of ibrutinib is 560 mg PO daily, continuous
- **Lymphocytosis**
  - ➤ **CLL:** Upon initiation of ibrutinib, transient increase in absolute lymphocyte count is expected in most patients, which does not signify disease progression. This onset of isolated lymphocytosis occurs during the first few weeks of ibrutinib therapy and may persist for several weeks on treatment.
  - ➤ **MCL:** Upon initiation of ibrutinib, transient increase in absolute lymphocyte counts occurred in 33% of patients. The onset of isolated lymphocytosis occurs during the first few weeks of ibrutinib therapy and resolves by a median of 8 weeks.
- **Grade >2 bleeding events were observed in 6% of patients on ibrutinib; the mechanism is not well-understood. Consider the benefit-risk of ibrutinib in patients requiring anti-platelet or anticoagulant therapies. Clinical trials excluded subjects on concurrent warfarin.**
- **New onset atrial fibrillation was reported in <5%, associated with ibrutinib administration.**

IDELALISIB

- **The recommended dose of idelalisib is 150 mg PO twice daily, per prescribing recommendations.**
- **Fatal and/or serious hepatotoxicity, severe diarrhea or colitis, pneumonitis, and intestinal perforation have been observed in patients treated with idelalisib.**
  - ➤ **Hepatotoxicity:** Monitor hepatic function prior to and during treatment. Interrupt (if ALT/AST > 5 x ULN (upper limit of normal) and when resolved may resume at a reduced dose (100 mg PO twice daily).
  - ➤ **Diarrhea or Colitis:** Monitor for the development of severe diarrhea or colitis. Interrupt until resolution and then reduce or discontinue idelalisib. Severe diarrhea and colitis can be managed with systemic or nonabsorbable steroids.
  - ➤ **Pneumonitis:** Monitor for pulmonary symptoms and bilateral interstitial infiltrates. Discontinue idelalisib.
  - ➤ **Intestinal perforation:** Discontinue idelalisib if intestinal perforation is suspected.
- **Lymphocytosis**
  - ➤ **CLL:** Upon initiation of idelalisib, transient increase in absolute lymphocyte count is expected in most patients, which does not signify disease progression. This onset of isolated lymphocytosis occurs during the first few weeks of idelalisib therapy and may persist for several weeks on treatment.

Co-administration with CYP3A inhibitors and inducers[2,3]

- Avoid concomitant administration of ibrutinib/idelalisib with strong or moderate inhibitors of CYP3A.
  - ➤ For strong CYP3A inhibitors used short-term (e.g., antifungals and antibiotics for 7 days or less, e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin) consider interrupting ibrutinib/idelalisib therapy during the duration of inhibitor use. Avoid strong CYP3A inhibitors that are needed chronically.
  - ➤ If a moderate CYP3A inhibitor must be used, reduce the ibrutinib/idelalisib dose. Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of ibrutinib/idelalisib toxicity.
- Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin and St. John's Wort). Consider alternative agents with less CYP3A induction.

[1]Please refer to package insert for full prescribing information and monitoring for adverse reactions, available at www.fda.gov.
[2]Ibrutinib package insert. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/205552lbl.pdf.
[3]Idelalisib package Insert. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206545lbl.pdf.

> **Note:** All recommendations are category 2A unless otherwise indicated.
> **Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

NHODG-E

Classification

Table 1

WHO Classification of the Mature B-Cell, T-Cell, and NK-Cell Neoplasms (2008)

Mature B-Cell Neoplasms
- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- *Splenic lymphoma/leukemia, unclassifiable**
  - *Splenic diffuse red pulp small B-cell lymphoma**
  - *Hairy cell leukemia-variant**
- Lymphoplasmacytic lymphoma
  - Waldenström's macroglobulinemia
- Heavy chain diseases
  - Alpha heavy chain disease
  - Gamma heavy chain disease
  - Mu heavy chain disease
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extraosseous plasmacytoma
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT type)
- Nodal marginal zone lymphoma
  - *Pediatric nodal marginal zone lymphoma**
- Follicular lymphoma
  - *Pediatric follicular lymphoma**
- Primary cutaneous follicle center lymphoma
- Mantle cell lymphoma

Diffuse large B-cell lymphoma (DLBCL), NOS
  - T-cell/histiocyte-rich large B-cell lymphoma
  - Primary DLBCL of the CNS
  - Primary cutaneous DLBCL, leg type
  - *EBV positive DLBCL of the elderly**
- DLBCL associated with chronic inflammation
- Lymphamatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK-positive large B-cell lymphoma
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
- Primary effusion lymphoma
- Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

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*The italicized histologic types are provisional entities, for which the WHO Working Group felt there was insufficient evidence to recognize as distinct diseases at this time.

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Classification

Table 1 continued

Mature T-Cell and NK-Cell Neoplasms
- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
  - ➤ *Chronic lymphoproliferative disorder of NK-cells**
- Aggressive NK cell leukemia
- Systemic EBV-positive T-cell lymphoproliferative disorder of childhood
- Hydroa vacciniforme-like lymphoma
- Adult T-cell leukemia/lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30-positive T-cell lymphoproliferative disorders
  - ➤ Lymphomatoid papulosis
  - ➤ Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous gamma-delta T-cell lymphoma
- *Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma**
- *Primary cutaneous CD4-positive small/medium T-cell lymphoma**
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large-cell lymphoma, ALK positive
- *Anaplastic large-cell lymphoma, ALK negative**

Hodgkin Lymphoma
- Nodular lymphocyte-predominant Hodgkin lymphoma
- Classical Hodgkin lymphoma
  - ➤ Nodular sclerosis classical Hodgkin lymphoma
  - ➤ Lymphocyte-rich classical Hodgkin lymphoma
  - ➤ Mixed cellularity classical Hodgkin lymphoma
  - ➤ Lymphocyte-depleted classical Hodgkin lymphoma

Post-Transplant Lymphoproliferative Disorders (PTLD)
- Early lesions
  - ➤ Plasmacytic hyperplasia
  - ➤ Infectious mononucleosis-like PTLD
- Polymorphic PTLD
- Monomorphic PTLD (B- and T/NK-cell types)[#]
- Classical Hodgkin lymphoma type PTLD[#]

Adapted from Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (Eds): World Health Organization Classification of Tumours of the Haematopoietic and Lymphoid Tissues. IARC, Lyon 2008.

*The italicized histologic types are provisional entities, for which the WHO Working Group felt there was insufficient evidence to recognize as distinct diseases at this time.

[#]These lesions are classified according to the leukemic or lymphoma to which they correspond.

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Staging

Table 2

Cotswolds Modification of Ann Arbor Staging System

Stage	Area of Involvement
I	Single lymph node group
II	Multiple lymph node groups on same side of diaphragm
III	Multiple lymph node groups on both sides of diaphragm
IV	Multiple extranodal sites or lymph nodes and extranodal disease
X	Bulk >10 cm
E	Extranodal extension or single isolated site of extranodal disease
A/B	B symptoms: weight loss >10%, fever, drenching night sweats

From: Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol 1989;7:1630-1636.

Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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Overview

Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of lymphoproliferative disorders originating in B-lymphocytes, T-lymphocytes or natural killer (NK) cells. In the United States, B-cell lymphomas are diagnosed in 80% to 85% of people with 15% to 20% being T-cell lymphomas. NK-cell lymphomas are very rare. In 2014, an estimated 70,800 people will be diagnosed with NHL and there will be approximately 19,020 deaths due to the disease; cases of chronic lymphocytic leukemia (CLL) are estimated separately.[1] NHL is the seventh leading site of new cancer cases among men and women, accounting for 4% of new cancer cases and 3% of cancer-related deaths.[1]

The incidence of NHL has increased dramatically between 1970 and 1995; the increase has moderated since the mid-90s. This increase has been attributed partly to the human immunodeficiency virus (HIV) epidemic and the development of AIDS-related NHL. However, much of the increase in incidence has been observed in patients in their sixth and seventh decades; a large part of this increase incidence has paralleled a major decrease in mortality from other causes. The median age of individuals with NHL has risen in the last two decades.[2] As a result, patients with NHL may also have significant comorbid conditions, which complicate treatment options.

The National Comprehensive Cancer Network (NCCN®) Guidelines (NCCN Guidelines®) for NHL were developed as a result of meetings convened by a multidisciplinary panel of NHL experts, with the aim to provide recommendations on the standard diagnostic and treatment approaches based on the current evidence. The NCCN Guidelines and the following discussions focus on the recommendations for diagnostic workup, treatment, and surveillance strategies for the most common subtypes of NHL, in addition to a general discussion on the classification systems used in NHL and supportive care considerations.

Previous versions of the NCCN Guidelines for NHL included treatment recommendation for lymphoblastic lymphoma. The NCCN Guidelines for Acute Lymphoblastic Leukemia (ALL) should be consulted for the management of patients with lymphoblastic lymphoma.

The most common NHL subtypes that are covered in these NCCN Guidelines are listed below:

Mature B-cell lymphomas

- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)
- Hairy cell leukemia (HCL)
- Follicular lymphoma (FL)
- Diffuse large B-cell lymphoma (DLBCL)
- Burkitt lymphoma (BL)
- AIDS-related B-cell lymphoma
- Primary Cutaneous B-cell Lymphomas
- Marginal Zone lymphomas (MZL)
  - Extranodal MZL of mucosa associated lymphoid tissue (MALT lymphoma)
    - Gastric MALT lymphoma
    - Non-gastric MALT lymphoma
  - Nodal MZL
  - Splenic MZL
- Mantle cell lymphoma (MCL)

Mature T-cell and NK-cell lymphomas

- Peripheral T-cell lymphoma (PTCL)

- Mycosis fungoides (MF) and Sezary syndrome(SS)
- Adult T-cell leukemia/lymphoma (ATLL)
- Extranodal NK/T-cell lymphomas, nasal type (ENKL)
- T-cell prolymphocytic leukemia (T-PLL)
- Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders
- T-cell Large Granular Lymphocytic Leukemia

Post-Transplant Lymphoproliferative Disorders (PTLD)

Classification

In 1956, Rappaport et al. proposed a lymphoma classification that was based on the pattern of cell growth (nodular or diffuse), and size and shape of the tumor cells.[3,4] This classification, though widely used in the Unites states, quickly became outdated with the discovery and the existence of distinct types of lymphocytes (B, T and NK). The Kiel classification became the first and most significant classification that applied this new information to the classification of lymphomas.[5-7] According to the Kiel classification, the lymphomas were divided into low-grade and high-grade based on the histological features. This classification was widely used in Europe. The use of different classification systems in clinical studies made it difficult to compare results from clinical studies. Hence, the International Working Formulation (IWF) for NHLs was developed to standardize the classification of lymphomas.

International Working Formulation Classification

The IWF classified NHL into three major categories as low, intermediate and high grade, based on the morphology and natural history.[8] This classification divided DLBCL into intermediate and high grade groups. However, these distinctions were not reproducible. Since this classification did not include immunophenotyping, the categories were

not reproducible.[9] In addition, after this classification was published many new diseases were described that were not included in the IWF classification.

Revised European American Classification

In 1994, the International Lymphoma Study Group (ILSG) developed the REAL classification, which classified lymphomas based on the cell of origin (B, T, or NK) and included morphology, immunophenotype, genetic and clinical features to define diseases.[10] In 1997, the International Lymphoma Classification Project performed a clinical evaluation of the Revised European American Classification (REAL) classification in a cohort of 1,403 cases of NHL.[11,12] The diagnosis of NHL was confirmed in 1,378 (98.2%) of the cases. This study identified the thirteen most common histological types, comprising about 90% of the cases of NHL in the United States. The findings were as follows: DLBCL, 31%; follicular lymphoma (FL), 22%; small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL), 6%; mantle cell lymphoma (MCL), 6%; peripheral T-cell lymphoma (PTCL), 6%; and mucosa associated lymphoid tissue (MALT) lymphoma, 5%. The remaining subtypes each occurred in less than 2% of cases. Importantly, in the United States more than 50% of cases of lymphoma are either DLBCL or FL. The study investigators concluded that the REAL classification can be readily applied and identifies clinically distinctive types of NHL.

World Health Organization Classification

In 2001, the World Health Organization (WHO) updated the classification of hematopoietic and lymphoid neoplasms.[13,14] The 2001 WHO classification applied the principles of REAL classification and represented the first international consensus on classification of hematologic malignancies. The REAL/WHO classification of NHL

includes many entities not recognized by the IWF.[13,14] After consideration of cell of origin (B, T, or NK), the classification subdivides lymphomas into those derived from precursor lymphocytes versus those derived from mature lymphocytes. The classification is further refined based on immunophenotype, genetic, and clinical features. These considerations have aided in defining active treatment for specific subtypes of lymphoma.

In 2008, the International T-cell lymphoma Project evaluated the WHO classification of T-cell lymphoma in a cohort of 1,314 cases of PTCL and natural killer/T-cell lymphomas (NKTCL). The diagnosis of PTCL or NKTCL was confirmed in 1,1,53 cases (88%). The most common subtypes were PTCL-not otherwise specified (NOS; 25.9%), angioimmunoblastic lymphoma (18.5%), NKTCL (10.4%), adult T-cell leukemia/lymphoma (ATLL; 9.6%), anaplastic large cell lymphoma (ALCL), ALK-positive (6.6%) and ALCL, ALK-negative (5.5%).[15] The findings of this study validated the utility of the WHO classification for defining subtypes of T-cell lymphomas.

The WHO classification was updated again in September 2008 to add new diseases and subtypes that have been recognized in the past decade, and to better define some of the heterogeneous and ambiguous categories based on the recent advances.[16,17] Genetic features, detected by cytogenetics or fluorescence in-situ hybridization (FISH) are increasingly important in defining specific NHL subtypes. In addition, detection of viruses, particularly Epstein-Barr virus, HHV8 and HTLV1, is often necessary to establish a specific diagnosis.

2008 WHO Classification of Mature B-cell Lymphomas

CLL/SLL

The updated classification includes the definition issued by the International Working Group on CLL (IWCLL).[18] The diagnosis of CLL requires the presence of monoclonal B lymphocytes ≥ 5 x 10^9/L in peripheral blood and the clonality of B cells should be confirmed by flow cytometry. The presence of fewer than 5000/mm^3 B-lymphocytes in the absence of lymphadenopathy, organomegaly or other clinical features is defined as monoclonal B-lymphocytosis (MBL). CLL requiring treatment develops in individuals with CLL-phenotype MBL and with lymphocytosis at the rate of 1.1% per year.[19]

Follicular Lymphoma

In FL, pathological grading according to the number of centroblasts is considered to be a clinical predictor of outcome. In the 2001 WHO classification, three grades were recommended: FL1, FL2, and FL3; FL3 could be optionally stratified into 3A (centrocytes still present) or 3B (sheets of centroblasts). However, clinical outcomes for patients with FL1 and FL2 do not differ and this classification was deemed unreliable. Therefore, in the updated 2008 WHO classification, these grades are grouped under a single grade (FL1-2). Hans et al reported that there was no difference in survival outcomes between patients with Grade 3A and 3B FL, whereas patients with FL3 with more than 50% diffuse component have an inferior survival similar to the survival of those with DLBCL.[20] FL3B with cytogenetic abnormalities of BCL6 (at 3q27) are thought to be genetically more akin to germinal center type DLBCL than FL1-3A, and is associated with a more aggressive clinical course. Patients with FL3B with BCL2 translocation appear to have a clinical course similar to patients with FL1-3A.[21] Since FL3B is rare, the clinical behavior of FL3 in most studies is based mainly on FL3A cases. The 2008 WHO classification mandates stratifying FL3 into either 3A or 3B. FL is thus still divided into three grades (FL1-2, FL3A and FL3B) based on the number of centroblasts. Any diffuse areas in FL should be given a separate diagnosis of DLBCL, if it meets the criteria for FL3A or 3B.

Pediatric-type FL, primary intestinal FL, other extranodal FLs and follicular lymphoma "in situ" (FLIS) are the other variants that are included under FL.

Pediatric-type follicular lymphoma: Pediatric-type FL is considered a rare variant of FL in the 2008 WHO classification and is generally characterized by lack of *BCL2* rearrangement and t(14,18), which constitute the genetic hallmark of conventional FL seen in adults.[22-26] Pediatric-type FL has a better prognosis than adult FL and is often cured with minimal therapy.

Primary intestinal follicular lymphoma: FL of the gastrointestinal tract is a recently described entity, which is common in the small intestine with the vast majority of cases occurring in the duodenum. The morphology, immunophenotype, and genetic features are similar to those of nodal FL. However, most patients have clinically indolent and localized disease. Survival appears to be excellent even without treatment.

Other extranodal follicular lymphoma: In many of the other extranodal sites, the morphology, immunophenotype, and genetic features are similar to those of nodal FL. Patients usually have localized disease and systemic relapses are rare.

Follicular Lymphoma "in situ": FLIS is characterized by the preservation of the lymph node architecture, with the incidental finding of focal strongly positive staining for BCL2 (restricted to germinal centers) and CD10 in the involved follicles, and the detection of t(14;18) by FISH.[23,27-29] FLIS has been reported in patients with prior FL or concurrent FL (at other sites), as well as in individuals with no known history of FL.[23,27,28] The occurrence of FLIS in the general population appears to be rare.

Primary Cutaneous Follicle Center Lymphoma (PC-FCL)
This is a new category in the 2008 classification and is defined as a tumor of neoplastic follicle center cells, including centrocytes and variable numbers of centroblasts, with a follicular, follicular and diffuse or a diffuse growth pattern. PC-FCL is the most common B-cell lymphoma of the skin and it is classified as a distinct entity in the EORTC classification of cutaneous lymphomas.[30] Gene expression profiling studies have also provided evidence in support of this classification.[31] PC-FCL presents as a solitary or localized skin lesion on the scalp, forehead or the trunk. It is characterized by an indolent course and rarely disseminates to extracutaneous sites. PC-FCL is consistently BCL6-positive, may be CD10-positive in cases with a follicular growth pattern. BCL2 is often either negative or dim (predominantly seen in cases with a follicular growth pattern). PC-FCL has an excellent prognosis with a 5-year survival rate of 95%.[30,32] PC-FCL must be distinguished from primary cutaneous DLBCL, leg type, which is not always possible histologically, and can be identified by expression of IRF4/MUM1, is strongly BCL2+ and has a more unfavorable prognosis.[33,34]

Diffuse Large B-cell Lymphomas
Some of the new categories of DLBCL are defined by extranodal primary sites and the association with viruses such as EBV or HHV8. Two borderline categories have also been included to incorporate cases in which it is not possible distinguish between adult Burkitt lymphoma (BL) and DLBCL, and primary mediastinal large B-cell lymphoma (PBML) and nodular sclerosis classical Hodgkin lymphoma (NSCHL). The ALK-positive DLBCL, plasmablastic lymphoma and primary effusion lymphoma are considered as distinct entities. The 2008 classification also has new category of large B-cell lymphoma arising in HHV8-associated multicentric Castleman's disease.

DLBCL, Not Otherwise Specified (NOS)

The 2008 classification has included DLBCL, NOS as a new category to include GCB and ABC subtypes as well as other DLBCL cases that do not belong to any of the four specific subtypes (T-cell/histiocyte rich large B-cell lymphoma, primary CNS DLBCL, primary cutaneous DLBCL ("leg type") or EBV+ DLBCL of the elderly).

Gene expression profiling (GEP) has been used to identify distinct subtypes of DLBCL: germinal center B-cell (GCB) subtype, activated B-cell (ABC) subtype, primary mediastinal B-cell lymphoma (PMBL), and type 3 which includes cases that cannot be classified as GCB, ABC, or PMBL subtypes.[35] GEP is not yet recommended for routine clinical use. Immunostaining algorithms have been developed to differentiate between GCB and ABC subtypes using a combination of CD10, BCL6, IRF4/MUM1, GCET1 and FOXP1,[36,37] and the outcome appears improved in GCB patients, though subtype does not impact choice of therapy at the present time.[38-40]

B-cell Lymphoma, Intermediate between BL and DLBCL

BL is characterized by t(8;14), which results in the juxtaposition of *MYC* gene from chromosome 8 with the immunoglobulin heavy chain variable (*IGHV*) region on chromosome14 and variant translocations involving *MYC* and the immunoglobulin light chain genes.[41] Nevertheless, *MYC* translocations also occur in DLBCL. GEP studies have confirmed that the distinction between BL and DLBCL is not reliably reproducible with the use of the current criteria of morphology, immunophenotype, and genetic abnormalities.[42,43] Mature aggressive B-cell lymphomas without a molecular BL signatures (non-mBL) with *MYC* rearrangements[43] as well as those with both t(8;14) and t(14;18) translocations are associated with a poor prognosis.[44]

This provisional category replaces the "Atypical Burkitt Lymphoma" that was included in the 2001 WHO classification. The new category includes lymphomas with features of both DLBCL and BL, but or biological and clinical reasons should not be diagnosed as DLBCL or BL. Lymphomas in this provisional category include those that are morphologically intermediate between BL and DLBCL with immunophenotype suggestive of BL (CD10-positive, BCL6-positive, BCL2-negative and IRF4/MUM1-negative or weakly positive), lymphomas that are morphologically similar to BL but are strongly BCL2-positive and those with both *MYC* and *BCL2* rearrangements ("double hit") and complex karyotypes.

B-cell Lymphoma Intermediate between PMBL and NSCHL

PMBL has been recognized as a subtype of DLBCL based on its distinctive clinical and morphological features. NSCHL is the most common form of HL. Both tumors occur in the mediastinum and affect adolescents and young adults. GEP studies strongly support a relationship between PMBL and CHL. About a third of the genes that were more highly expressed in PMBL were also characteristically expressed in CHL cells.[45] Traverse-Glehen, et al., reported borderline cases with biologic and morphologic features of both CHL and B-cell NHL, known as "mediastinal gray zone lymphomas".[46]

This provisional category includes lymphomas with overlapping features between CHL and DLBCL, especially PBML. Those cases that morphologically resemble NSCHL have a strong expression of CD20 and other B-cell associated markers. Those cases that resemble PBML may have dim or no expression of CD20, strong expression of CD30 and CD15. These lymphomas have a more aggressive course and poorer outcome than either CHL or PBML.

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Primary Cutaneous DLBCL, Leg Type (PC-DLBCL)

PC-DLBCL, leg type, is an unusual form of DLBCL composed of large transformed B cells most commonly arising on the leg (85-90%) although it can arise at other sites (10-15%).[32] These tumors arise from post-germinal center B-cell with expression of CD20, IRF4/MUM1, FOXP1, and BCL2; many cases express BCL6 and lack expression of CD10.[32,47,48] These tumors can disseminate to non-cutaneous sites, including the CNS. Studies have reported the development of extracutaneous relapse in 17-47% of patients with PC-DLBCL.[32,49,50] In a study in patients with PC-DLBCL (N=60), CNS was the most common site of visceral progression, occurring in 27% of patients with extracutaneous relapse (or in 12% of all patients on this study).[49] The high frequency of extracutaneous relapse in PC-DLBCL results in a poorer prognosis than the other cutaneous B-cell lymphomas, especially when the presentation involves multiple cutaneous lesions.[49]

2008 WHO Classification of Mature T-cell and NK-cell Lymphomas

The 2008 WHO classification has adapted the EOTRC classification for cutaneous T-cell lymphomas.[30] The new categories include primary cutaneous gamma-delta T-cell lymphoma, primary cutaneous aggressive epidermotropic CD9-positive cytotoxic T-cell lymphoma and primary cutaneous small/medium CDE4-positive T-cell lymphoma. Anaplastic large cell lymphoma (ALCL), ALK-negative is now separated out from PTCL-NOS as a provisional entity.

ALCL

ALCL accounts for less than 5% of all cases of NHL. There are now three distinctly recognized subtypes of ALCL: ALCL, ALK-positive, ALCL, ALK-negative and primary cutaneous ALCL. Primary cutaneous ALCL is a distinct subtype of mature T-cell lymphoma. ALK-positive ALCL is most common in children and young adults. It is characterized by the over expression of anaplastic lymphoma kinase (ALK1) protein, resulting from t(2;5) in 40-60% of patients.[51,52] Although clinically aggressive, it is highly curable with CHOP chemotherapy. The distinction between ALK-positive and ALK-negative ALCL was not required in the 2001 WHO classification. It is now clear that ALK-positive ALCL is a well-defined clinicopathologic entity. The International Peripheral T-Cell Lymphoma Project reported that patients with ALK-positive ALCL had a superior outcome compared with those with ALK-negative ALCL [5-year failure-free survival (FFS): 60% vs. 36%; and 5-year overall survival (OS): 70% vs. 49%].[53] Contrary to prior reports, ALK-negative ALCL was associated with a better outcome than PTCL-NOS. The 5-year FFS (36% vs. 20%) and OS (49% vs. 32%) were superior compared with PTCL-NOS. A recent analysis from the GELA found that age and beta-2 microglobulin, not ALK1 expression, were the most significant prognostic factors of overall survival for patients with ALCL; however, age was very closely associated with ALK1 expression.[54] Patients with primary cutaneous ALCL had a very favorable 5-year OS (90%) despite being negative for ALK1; the 5-year FFS rate was 55%. The findings of this study confirmed that ALK-negative ALCL should be separated from both ALK-positive ALCL and PTCL-NOS. Based on the recent findings, the 2008 WHO classification has included a provisional category for ALK-negative ALCL. It is morphologically identical to ALK-positive ALCL, with a strong and diffuse expression of CD30, no expression of B-cell antigens and absence of ALK1. The prognosis is intermediate between that of ALK-positive ALCL and PTCL-NOS.

Response Criteria

The International Working Group (IWG) published the guidelines for response criteria for lymphoma in 1999. These response criteria are based on the reduction in the size of the enlarged lymph node as

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measured by CT scan and the extent of bone marrow involvement that is determined by bone marrow aspirate and biopsy.[55] These guidelines were revised in 2007 by the International Harmonization Project to incorporate IHC, flow cytometry and 18-flourodeoxyglucose (FDG)-positron emission tomography (PET) scans in the definition of response for lymphoma.[56] In the revised guidelines, the response category of complete response uncertain (CRu) was essentially eliminated because residual masses were defined as a partial response (PR) or a complete response (CR) based on the result of a PET scan. Using the revised system, response is categorized as CR, PR, stable disease (SD) and relapsed disease or progressive disease (PD).

However, the application of PET to responses is limited to histologies where there is reliable FDG uptake in active tumor. However, the revised response criteria have thus far only been validated for DLBCL and Hodgkin lymphoma. The application of the revised response criteria to other histologies requires validation and the original IWG guidelines should be used. Of note, the IWG response criteria may not be applicable for several of the tumor subtypes included in the NCCN Guidelines. Tumor specific response criteria are included in the guidelines for CLL/SLL, MF/SS, ATLL, HCL and T-PLL.

Diagnosis

In all cases of NHL, the most important first step is an accurate pathologic diagnosis. The basic pathological evaluation is the same in each Guidelines (by tumor subtype), although some further evaluation may be useful in certain circumstances to clarify a particular diagnosis; these are outlined in the pathological evaluation of the individual Guidelines.

An incisional or excisional lymph node biopsy is recommended to establish the diagnosis of NHL. Core needle biopsy is discouraged unless the clinical situation dictates that this is the only safe means of obtaining diagnostic tissue. Fine needle aspiration (FNA) biopsy is widely used in the diagnosis of malignant neoplasms, but its role in the diagnosis of lymphoma is still controversial.[57,58] Since the revised REAL/WHO classification is based on both morphology and immunophenotyping, FNA alone is not acceptable as a reliable diagnostic tool for NHL. However, its use in combination with ancillary techniques may provide precise diagnosis thereby obviating the need for a more invasive biopsy in highly selected circumstances. Recent studies have shown that the diagnostic accuracy of FNA improves significantly when it is used in combination with IHC and flow cytometry.[59-61]

In the NCCN Guidelines, FNA alone is not suitable for an initial diagnosis of NHL, though it may be sufficient to establish relapse. However, in certain circumstances, when a lymph node is not easily accessible, a combination of core biopsy and FNA in conjunction with appropriate ancillary techniques [PCR for *IGHV* and/or T-cell receptor (*TCR*) gene rearrangements; FISH for major translocations; immunophenotypic analysis] may be sufficient for diagnosis. This is particularly true for the diagnosis of CLL. In other entities presenting in leukemic phase, such as FL or MCL, a biopsy is still preferred to clarify histological subtype.

Immunophenotypic analysis is essential for the differentiation of various subtypes of NHL to establish the proper diagnosis. It can be performed by flow cytometry and/or IHC; the choice depends on the antigens as well as the expertise and resources available to the hematopathologist. In some cases flow cytometry and IHC are complementary diagnostic tools.[62] Cytogenetic or molecular genetic

analysis may be necessary under certain circumstances to identify the specific chromosomal translocations that are characteristic of some NHL subtypes or to establish clonality.

After the publication of the 2008 WHO Classification, the NHL Guidelines panel developed a series of algorithms for the use of immunophenotyping in the diagnosis of mature lymphoid neoplasms. These algorithms were developed to provide guidance for surgical pathologists as well as an aid to the clinician in the interpretation of pathology reports and they should be used in conjunction with clinical and pathological correlation. See *Immunophenotyping/Genetic Testing* in the guidelines.

Workup

Essential workup procedures include a complete physical exam with particular attention to node bearing areas and the size of liver and spleen, symptoms present, performance status, laboratory studies including CBC, serum lactate dehydrogenase (LDH), hepatitis B virus testing (see below), comprehensive metabolic panel, and CT chest/abdominal/pelvic with oral and intravenous contrast (unless co-existent renal insufficiency). MUGA scan or echocardiograms are recommended when anthracyclines and anthracenedione containing regimens are used. Bone marrow biopsy with or without aspirate is essential in all cases where treatment is considered; however, there are circumstances where it may be deferred (see below). Due the risk of hepatitis B reactivation, the panel has included hepatitis B testing (hepatitis B surface antigen and hepatitis B core antibody) as part of essential workup prior to initiation of treatment in all patients who will receive anti CD20 monoclonal antibody-based regimens. Furthermore, hepatitis B reactivation has been reported with chemotherapy alone and testing should be considered in anyone with a risk factor (e.g.

blood transfusion, IV drug abuse) or if from a region with a non-negligible prevalence of hepatitis B infection (see *"Hepatitis B Reactivation"* in the Supportive Care section below). Hepatitis C testing is needed in high-risk patients and patients with splenic marginal zone lymphoma.

Optional procedures (depending on specific lymphoma type) include beta-2-microglobulin, CT or PET-CT scans, endoscopic ultrasound (gastric MALT lymphoma), head CT or brain MRI and lumbar puncture to analyze cerebrospinal fluid (MCL and DLBCL). Discussion of fertility issues and sperm banking should be addressed in the appropriate circumstances.[63]

Bone marrow biopsy is usually included in the workup for all patients with NHL with the exception of SLL/CLL when there is a clonal lymphocytosis identified by flow cytometry. Bone marrow involvement occurs in 39% of low-grade, 36% of intermediate grade and 18% of high-grade lymphomas. Bone marrow involvement was associated with significantly shorter survivals in patients with intermediate or high-grade lymphomas.[64] In a retrospective analysis, the incidence of bone marrow involvement and the parameters predicting bone marrow involvement were analyzed in 192 patients with stage I and II in DLBCL.[65] Overall incidence of BM involvement was 3.6%. The authors concluded that bone marrow biopsy may be safely omitted in selected patients with early stage DLBCL.[65] In cutaneous B-cell lymphomas, bone marrow biopsy is essential for PC-DLBCL, leg type, since this is an aggressive lymphoma that will probably require systemic treatment, whereas the role of bone marrow biopsy in the PC-FCL and PC-MZL subtypes is less clear. Recent studies have indicated that bone marrow biopsy is an essential component of staging in patients with PC-FCL first presenting in the skin, whereas it appears to have limited

value in patients with MZL presenting in the skin, and may be considered only in selected cases.[66,67]

In the NCCN Guidelines, bone marrow biopsy with or without aspirate is included as part of essential workup for all lymphomas. However, in patients with low bulk indolent disease with radiographic clinical stage III disease, an initial staging bone marrow evaluation can be deferred if observation is recommended as it will not change the clinical recommendations. However, in the evaluation of potentially early stage indolent lymphoma (stage I or II), bone marrow biopsy is essential; some panel members advocate bilateral core biopsies in this situation.[68] Bilateral cores are recommended if radioimmunotherapy is considered.

FDG-PET scan has been used for initial staging, restaging and follow-up of patients with NHL.[69] In a meta-analysis study, PET showed a high positivity and specificity when used for the staging and restaging of patients with lymphoma.[70] FDG-PET is nearly universally positive at diagnosis in Hodgkin lymphoma, DLBCL, and follicular lymphoma,[71] about 90% in T-cell lymphoma[72] and nodal MZL but less sensitive for extra-nodal MZL.[73] However, a number of benign conditions including sarcoid, infection, and inflammation can result in false-positive PET scans complicating the interpretation. Lesions smaller than 1 cm are not reliably visualized with PET scans. PET scan is now part of pre-treatment evaluation in Hodgkin lymphoma and DLBCL and may be useful in selected cases in other histologies. The pre-treatment PET is particularly important to aid in the interpretation of post-treatment response evaluation according to new response criteria (see above). Although PET scans may detect additional disease sites at diagnosis, the clinical stage is modified only in 15-20% of patients and a change in treatment in only 8% of

patients. PET scan has generally been used in conjunction with diagnostic CT scans.

Integrated PET-CT has largely replaced the dedicated CT scans in the United States. This diagnostic study has distinct advantages in both staging and restaging compared to full-dose diagnostic CT or PET alone.[74,75] In a retrospective study, PET-CT performed with low-dose non-enhanced CT was found to be more sensitive and specific than the routine contrast-enhanced CT in the evaluation of lymph node and organ involvement in patients with Hodgkin disease or high-grade NHL.[75] Preliminary results of another recent prospective study (47 patients; patients who had undergone prior diagnostic CT were excluded) showed a good correlation between low-dose unenhanced PET-CT and full-dose enhanced PET-CT in the evaluation of lymph nodes and extranodal disease in lymphomas.[74] However, the lack of intravenous contrast and the diminished resolution can make it difficult in some cases to interpret the anatomical localization and significance of FDG-avid sites. Further studies are needed to determine if PET-CT scans can replace diagnostic CT scans in the initial staging and response evaluation of lymphomas. The panel has included PET-CT scan as an optional workup procedure for selected patients.

Supportive Care

Supportive care remains an important component of managing patients with NHL, particularly during active therapy. Supportive care measures for NHL may include (but are not limited to) management of infectious complications, management of tumor lysis syndrome, and use of myeloid growth factors or blood product transfusions. These measures may help to maximize the benefit of NHL therapy for patients by enhancing tolerability, reducing treatment-related toxicities, and ensuring timely delivery of planned treatment courses. Patients with

hematologic malignances are at increased risk for infectious complications due to profound immunosuppression stemming from myelosuppressive therapy and/or the underlying malignancy. For example, reactivation of latent viruses may occur in the setting of significant immunosuppression in patients with NHL.

Viral Reactivation and Infections

Hepatitis B Virus Reactivation

Hepatitis B virus (HBV) reactivation has been reported in patients treated with chemotherapy with or without immunotherapy agents.[76-82] HBV carriers with lymphoid malignancies have a high risk of HBV reactivation and disease,[83] especially those treated with anti-CD20 monoclonal antibodies (e.g., rituximab, ofatumumab).[84] Cases of liver failure and death associated with HBV reactivation have occurred in patients receiving rituximab-containing regimens.[84]

Testing for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) can determine the HBV status of an individual. Because of the widespread use of the hepatitis B vaccine, hepatitis B surface antibody (HBsAb) positivity is of limited value; however, in rare cases, HBsAb levels can help to guide therapy. Patients with malignancies who are positive for either HBsAg or HBcAb are at risk for HBV reactivation with cytotoxic chemotherapy; approximately 20% to 50% of patients with HBsAg positivity and 3% to 45% with HBcAb positivity develop HBV reactivation.[76,77,79,82,85-92] False-negative HBsAg results may occur in chronic liver disease; therefore, patients with a history of hepatitis in need of chemotherapy should be assessed by viral load measurement.[93] HBsAb positivity is generally equated with protective immunity, although reactivated HBV disease may occur in the setting of significant immunosuppression in HBcAb-positive individuals.[77,94] In patients with B-cell lymphoid malignancies treated with rituximab-containing regimens, HBV reactivation was observed in

patients with HBcAb positivity (with or without HBsAb positivity), even among those who were HBsAg negative prior to initiation of treatment.[79,87,92] A recent meta-analysis and evaluation of the FDA safety reports concerning HBV reactivation in patients with lymphoproliferative disorders reported that HBcAb positivity was correlated with increased incidence of rituximab-associated HBV reactivation.[86] Vaccination against HBV should be strongly considered In HBV-naïve patients (i.e., negative for HBsAg, HBsAb, and HBcAb).[77,95]

Recommended strategies for the management of HBV reactivation in patients with hematologic malignances undergoing immunosuppressive therapy include upfront antiviral prophylaxis or pre-emptive therapy. Prophylactic approaches involve treating patients who are HBsAg-positive or HBcAb-positive with prophylactic antiviral therapy, regardless of viral load or presence of clinical manifestations of HBV reactivation. The alternative strategy of pre-emptive therapy involves close surveillance with a highly sensitive quantitative assay for HBV, combined with antiviral therapy upon a rising HBV DNA load.[77] Antiviral prophylaxis with lamivudine has been shown to reduce the risks for HBV reactivation in HBsAg-positive patients with hematologic malignances treated with immunosuppressive cytotoxic agents.[83,96-99] A small randomized study in HBsAg-positive patients with lymphoma (N=30) showed that antiviral prophylaxis with lamivudine was superior to deferred pre-emptive therapy (i.e., antivirals given at the time of serological evidence of HBV reactivation based on viral DNA in serum samples).[96] HBV reactivation occurred in 53% of patients in the deferred therapy arm compared with none in the prophylaxis arm. In a meta-analysis of clinical trials evaluating the benefit of lamivudine prophylaxis in HBsAg-positive lymphoma patients treated with immunosuppressive regimens, prophylaxis resulted in significant

reductions in HBV reactivation (risk ratio=0.21; 95% CI, 0.13–0.35) and a trend for reduced HBV-related deaths (risk ratio=0.68; 95% CI, 0.19–2.49) compared with no prophylaxis.[99] Recent studies have shown entecavir to be more effective than lamivudine in preventing rituximab-associated HBV reactivation.[100-102] In a prospective study that compared the efficacy of antiviral prophylaxis with entecavir and lamivudine in HBsAg-positive patients with newly diagnosed DLBCL treated with R-CHOP chemoimmunotherapy (n = 229), entecavir was associated with significantly lower rates of hepatitis (8.2% vs 23.3%, P =.022), HBV reactivation(6.6% vs 30.0%, P =.001), delayed HBV-related hepatitis (0% vs 8.3%, P =.027) and disruption of chemotherapy (1.6% vs 18.3%, P =.002).[100] The results of another randomized controlled trial also showed that entecavir prophylaxis (before initiation of chemotherapy to 3 months after completion of chemotherapy) was more effective in preventing HBV-reactivation than the control (initiation of entecavir therapy at the time of HBV reactivation and HBsAg reverse seroconversion after chemotherapy).[101] The cumulative HBV reactivation rates at months 6, 12, and 18 after chemotherapy were 8%, 11.2%, and 25.9%, respectively, in the control group, and 0%, 0%, and 4.3% in the entecavir prophylaxis (P = .019).

Although prophylaxis with lamivudine has been evaluated in the setting of immunosuppressive anti-tumor therapy (as mentioned above), the optimal antiviral strategy remains unclear. Concerns over the development of resistance to lamivudine exist.[103-107] Adefovir combined with lamivudine has been evaluated in patients with lamivudine-resistant HBV infections.[108,109] Tenofovir has demonstrated superior antiviral efficacy compared with adefovir in randomized double-blind phase III studies in patients with chronic HBV infection, and may be the preferred agent in this setting, however, limited data are available regarding its use in patients with cancer.[110] Entecavir and telbivudine have also been

evaluated in randomized open-label studies with adefovir as the comparator in patients with chronic HBV infection, and both agents have shown improved antiviral activity compared with adefovir.[111,112]

The panel recommends HBsAg and HBcAb testing for all patients planned for treatment with anti-CD20 monoclonal antibody-containing regimens. In individuals who test positive for HBsAg and/or HBcAb, baseline quantitative PCR for HBV DNA should be obtained to determine viral load. However, a negative baseline PCR does not preclude the possibility of reactivation. In patients from areas with high HBV prevalence (Asia, Africa, Eastern Europe, and portions of South America) or regions where the prevalence is not known, all patients receiving immunotherapy, chemotherapy, or chemoimmunotherapy should be tested for HBsAg and HBcAb. Patients receiving intravenous immunoglobulin (IVIG) may be HBcAb positive as a consequence of IVIG therapy, although HBV viral load monitoring is recommended.[113]

Prophylactic antiviral therapy with entecavir is recommended for patients who are HBsAg positive and undergoing NHL therapy. Lamivudine prophylaxis should be avoided due to the risks for the development of resistance. For patients who are HBsAg negative but HBcAb positive, antiviral prophylaxis with entecavir is also the preferred approach; however, if these patients concurrently have high levels of HBsAb, they may be monitored with serial measurements of HBV viral load and treated with pre-emptive antivirals upon increasing viral load. During the treatment period, viral load should be monitored monthly with PCR and then every 3 months after completion of treatment. If viral load is consistently undetectable, prophylaxis with antivirals should be continued. If viral load fails to drop or a previously undetectable PCR becomes positive, consultation with a hepatologist and discontinuation of anti-CD20 antibody therapy is recommended.

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As mentioned above, several antiviral agents are available for prophylactic measures. The optimal choice will be driven by institutional standards or recommendation from hepatology or infectious disease consultant. The appropriate duration of prophylaxis remains undefined, but the panel recommended that surveillance and antiviral prophylaxis should be continued for up to 12 months after the completion of oncologic treatment.[77]

Hepatitis C Virus-associated B-cell NHL

Case-control studies have demonstrated a strong association between seropositivity for hepatitis C virus (HCV) and development of NHL, particularly for B-cell lymphomas.[114-122] In large population-based or multicenter case-control studies, prevalence of HCV seropositivity was consistently increased among patients with B-cell histologies including DLBCL and marginal zone lymphomas.[116,117,120,122] A retrospective study in patients with HCV infection (N=3209) showed that the cumulative incidence of developing malignant lymphomas was significantly higher among patients with persistent HCV infection compared with those who had sustained virologic response (SVR) to interferon-containing therapy (15-year incidence rate 2.6% vs. 0%; P=0.016).[123] Based on multivariate analysis, persistent HCV infection remained a significant independent factor associated with development of malignant lymphomas. This study suggested that achievement of SVR with interferon-based therapy may reduce the incidence of malignant lymphoma in patients with HCV infection.[123] Several published reports suggested that treatment with antivirals (typically, interferon with or without ribavirin) led to regression of NHLs in HCV-positive patients, which provide additional evidence for the involvement of HCV infection in the pathogenesis of lymphoproliferative diseases.[124-130] In a retrospective study in patients with NHL (N=343; indolent and aggressive histologies) who achieved a CR after chemotherapy, the subgroup of HCV-positive patients treated with antivirals (interferon and

ribavirin; n=25) had significantly longer disease-free survival compared with HCV-positive patients who did not receive antiviral therapy (n=44); the probability of relapse-free survival at 5-year follow up was 76% and 55%, respectively.[129] In addition, none of the patients with a SVR to antivirals (n=0 of 8) relapsed compared with 29% who did not respond to antivirals (n=5 of 17). In a multicenter retrospective study from a large series of HCV-positive patients with indolent NHL, antiviral therapy (interferon or pegylated interferon, with or without ribavirin), resulted in SVR in 78% of patients who received first-line antivirals (n=76) and in 56% of those who received antivirals as second-line therapy after failure of initial treatment (n=18).[130] Patients in this analysis did not require immediate treatment for their lymphoma. The overall hematologic response was 78% among both subgroups treated with antivirals in first line (CR in 47%) and in second line (CR in 27%). In the group of patients who received antivirals in first line, hematologic response was significantly associated with achievement of SVR.[130] Thus, in HCV-positive patients with indolent NHL not requiring immediate anti-tumor therapy with chemoimmunotherapy regimens, initial treatment with interferon (with or without ribavirin) appeared to induce lymphoma regression in a high proportion of patients. In HCV-positive patients with NHL who achieve a remission with anti-tumor therapy, subsequent treatment with antivirals may be associated with lower risk of disease relapse.

The optimal management of HCV-positive patients with NHL remains to be defined. Patients with indolent NHL and HCV seropositivity may benefit from antiviral treatment as initial therapy, as demonstrated in several reports.[124,126,128,130,131] In patients with aggressive NHL, an earlier analysis of pooled data from Groupe d'Etude des Lymphomes de l'Adulte (GELA) clinical studies (prior to the rituximab era) suggested that HCV seropositivity in patients with DLBCL was associated with

significantly decreased survival outcomes, due, in part, to severe hepatotoxicity among those with HCV infection.[132] Subsequent studies in the rituximab era showed that HCV seropositivity was not predictive of outcomes in terms of PFS or OS in patients with DLBCL.[133,134] However, the incidence of hepatotoxicity with chemoimmunotherapy was higher among HCV-positive patients, confirming the observation made from the GELA studies.

The treatment of chronic HCV infection has improved with the advent of newer antiviral agents, especially those that target carriers of HCV genotype 1. Direct acting antiviral agents (DAA) administered in combination with standard antivirals (pegylated interferon and ribavirin) have shown significantly higher rates of SVR compared with standard therapy alone in chronic carriers of HCV genotype 1.[135-138] Telaprevir and boceprevir are DAAs that were recently approved by the FDA for the treatment (in combination with pegylated interferon and ribavirin) of patients with HCV genotype 1 infection. The updated guidelines for the management of HCV infection from the American Association for the Study of Liver Diseases (AASLD) recommended that DAAs be incorporated into standard antiviral therapy for patients infected with HCV genotype 1.[139]

The panel recommends initial antiviral therapy in asymptomatic patients with HCV-positive low-grade B-cell NHL. For those with HCV genotype 1, triple antiviral therapy with inclusion of DAAs should be considered as per AASLD guidelines. Patients with HCV-positive aggressive B-cell NHL should initially be treated with appropriate chemoimmunotherapy regimens according to the NCCN Guidelines for NHL. Liver function and serum HCV RNA levels should be closely monitored during and after chemoimmunotherapy for development of hepatotoxicity. Antiviral therapy should then be considered in patients who achieve a CR after completion of chemoimmunotherapy.

Cytomegalovirus Reactivation

Cytomegalovirus (CMV) reactivation may occur among patients with lymphoproliferative malignancies (most commonly, CLL/SLL) receiving alemtuzumab therapy, and occurs most frequently between 3 to 6 weeks after initiation of therapy when T-cell counts reach a nadir.[140-143] CMV reactivation is a well-documented infectious complication in patients receiving treatment with alemtuzumab, occurring in up to 25% of treated patients.[142,144-148] Current management practices for prevention of CMV reactivation include the use of prophylactic ganciclovir (oral or IV) if CMV viremia is present prior to alemtuzumab therapy,[143] or pre-emptive use of these drugs when the viral load is found to be increasing during therapy.[140,149,150]

Several studies of alemtuzumab in patients with CLL have demonstrated the effectiveness of using routine CMV monitoring coupled with pre-emptive therapy with ganciclovir in preventing overt CMV disease.[140-142,151] A small randomized study in patients with lymphoproliferative disease treated with alemtuzumab-containing regimens (N=40) showed that upfront CMV prophylaxis with oral valganciclovir significantly reduced the incidence of CMV reactivation compared with oral valacyclovir (0% vs 35%; P=0.004).[143]

Patients with hematologic malignancies treated with alemtuzumab-containing regimens should be closely monitored and managed for potential development of CMV reactivation. To this end, periodic monitoring for the presence of CMV antigens using quantitative polymerase chain reaction (PCR) assays is an effective management approach.[149] The panel recommends routine surveillance for CMV viremia (every 2–3 weeks) during the treatment course with alemtuzumab and for 2 months following completion of alemtuzumab treatment.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a rare but serious and usually fatal CNS infection caused by reactivation of the latent (John Cunningham) JC polyoma virus. Cases of PML generally occur in severely immunocompromised individuals, as in the case of patients with AIDS. Patients with hematologic malignancies who have profound immunosuppression (due to the underlying disease and/or immunosuppressive therapies) are also at risk of developing PML. In a report of 57 cases from the Research on Adverse Drug Events and Reports project, 52 patients with lymphoproliferative disorders developed PML after treatment with rituximab and other treatments which included hematopoietic stem cell transplantation or chemotherapy with purine analogs or alkylating agents.[152] Median time from last rituximab dose to PML diagnosis was 5.5 months. Median time to death after PML diagnosis was 2 months. The case fatality rate was 90%.[152] The use of rituximab may be associated with an increased risk of PML in immunocompromised patients with lymphoproliferative malignancies.[153] Cases of PML have been reported with rituximab treatment (usually in combination with chemotherapy regimens) in patients with CLL/SLL or other types of NHL.[154-164] Patients with low CD4+ T-cells prior to or during anti-tumor treatment with rituximab-containing regimens may be particularly susceptible to PML.[152,154,155] Patients with NHL receiving treatment with another anti-CD20 monoclonal antibody ofatumumab,[165] or the anti-CD30 antibody-drug conjugate brentuximab vedotin, may also be at potential risk for PML.[166-168]

Development of PML is clinically suspected based on neurological signs and symptoms that may include confusion, motor weakness or poor motor coordination, visual changes, and/or speech changes.[152] PML is usually diagnosed with PCR of cerebrospinal fluid (CSF) or in some cases, by analysis of brain biopsy material. There is no effective treatment for PML. Patients should be carefully monitored for the development of any neurological symptoms. There is currently no consensus on pretreatment evaluations that can be undertaken to predict for the subsequent development of PML.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is a potentially serious complication of chemotherapy and is characterized by metabolic abnormalities caused by the abrupt release of intracellular contents into the blood resulting from cellular disintegration induced by chemotherapy. It is usually observed within 12 to 72 hours after start of chemotherapy.[169] Untreated TLS can induce profound metabolic changes resulting in cardiac arrhythmias, seizures, loss of muscle control, acute renal failure, and even death.

Cairo and Bishop have classified TLS into laboratory TLS and clinical TLS. Laboratory TLS is defined as a 25% increase in the levels of serum uric acid, potassium, or phosphorus or a 25% decrease in calcium levels.[170] Clinical TLS refers to laboratory TLS with clinical toxicity that requires intervention. Clinical complications may include renal insufficiency, cardiac arrhythmia, or seizures. The four primary electrolyte abnormalities of TLS are hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia. Symptoms associated with TLS may include nausea and vomiting, diarrhea, seizures, shortness of breath, or cardiac arrhythmias.

TLS is best managed if anticipated and when treatment is started prior to chemotherapy. The cornerstone of TLS management is hydration and the control of hyperuricemia. Allopurinol should be administered prior to the initiation of chemotherapy. Rasburicase is indicated in cases where the uric acid level remains elevated despite treatment with allopurinol or in patients with renal insufficiency. Electrolytes and

renal function should be monitored every 6 to 8 hours with appropriate interventions for hyperkalemia and hyperphosphatemia. Careful clinical monitoring will help to preempt complications, and in many cases, admission to ICU may be appropriate. Cardiac monitoring or serial ECG may be beneficial to identify early electrolyte-related cardiac abnormalities. Dialysis may be necessary in cases of anuric acute renal failure.

Allopurinol is a xanthine analog and a competitive inhibitor of xanthine oxidase, thereby blocking conversion of purine metabolites to uric acid. Allopurinol will decrease the formation of uric acid production and has been shown to reduce the incidence of uric-acid uropathy.[171] Since the drug inhibits new uric acid formation rather than reduce existing uric acid, it can take several days for elevated levels of uric acid to normalize after the initiation of treatment, which may delay the start of chemotherapy. Furthermore, allopurinol may lead to the accumulation of xanthine crystals in renal tubules leading to acute obstructive uropathy. Allopurinol will also reduce clearance of 6-mercaptopurine and high-dose methotrexate.

Rasburicase is a recombinant urate oxidase, which catalyzes the oxidation of uric acid to a highly soluble non-toxic metabolite that is readily excreted. It has been shown to be safe and highly effective in the prevention and treatment of chemotherapy-induced hyperuricemia in both children and adults with hematologic malignancies.[172] In an international compassionate use trial in patients at risk for TLS during chemotherapy (N=280 enrolled), rasburicase (0.20 mg/kg/day IV for 1–7 days) resulted in uric acid response in all evaluable patients (n=219; adults, n=97).[172] Among the subgroup of adults with hyperuricemia (n=27), mean uric acid levels decreased from pretreatment levels of 14.2 mg/dL to 0.5 mg/dL 24 to 48 hours after administration of last dose of rasburicase. Among adult patients at risk

for TLS (but without baseline hyperuricemia; n=70), mean uric acid levels decreased from 4.8 mg/dL to 0.4 mg/dL.[172] The GRAAL1 trial evaluated the efficacy and safety of rasburicase (0.20 mg/kg/day IV for 3–7 days, started on day 0 or day 1 of chemotherapy) for the prevention and treatment of hyperuricemia in adult patients with aggressive NHL during induction chemotherapy (N=100).[173] Prior to chemotherapy, 66% of patients had elevated lactate dehydrogenase (LDH) levels and 11% had elevated uric acid levels (>7.56 mg/dL). Uric acid levels were normalized and maintained within normal ranges during chemotherapy in all patients. Uric acid levels decreased within 4 hours after the first injection of rasburicase. In addition, serum creatinine levels and other metabolites were also controlled with the administration of rasburicase.[173]

A prospective, multicenter randomized phase III trial compared the efficacy and safety of rasburicase and allopurinol in adult patients with hematological malignancies at high or potential risk for TLS (N=275).[174] Patients were randomized to receive treatment with rasburicase alone (0.20 mg/kg/day IV for days 1–5; n=92), rasburicase combined with allopurinol (rasburicase 0.20 mg/kg/day IV for days 1–3; allopurinol 300 mg/day PO for days 3–5; n=92) or allopurinol alone (300 mg/day PO for days 1–5; n=91). The rate of uric acid response (defined as plasma uric acid levels ≤7.5 mg/dL for all measurements from days 3–5) was 87% for rasburicase, 78% for rasburicase combined with allopurinol and 66% for allopurinol.[174] The incidence of clinical TLS was similar across treatment arms, occurring in 3%, 3% and 4% of patients, respectively. The incidence of laboratory TLS was 21%, 27%, and 41%, respectively, with significantly lower incidence observed in the rasburicase arm compared with allopurinol (*P*=0.003). The response rate with rasburicase was superior to allopurinol in the overall study population (87% vs. 66%, as above; *P*=0.001) as well as in patients with high risk TLS (89% vs. 68%; *P*=0.001) and in patients

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with baseline hyperuricemia (90% vs. 53%; *P*=0.015). The median time to control for serum uric acid in hyperuricemic patients was 4 hours for rasburicase, 4 hours for rasburicase combined with allopurinol and 27 hours for allopurinol.[174] Potential hypersensitivity to study regimen was reported in 4% of patients in the rasburicase arm and 1% in the combination arm; no anaphylaxis or grade 4 hypersensitivity reactions were reported in this trial.[174] However, rasburicase can induce anaphylactic reactions. Other adverse reactions include methemoglobinemia and severe hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. A single fixed dose of rasburicase (6 mg)[175,176] or a single weight-based dose of rasburicase (0.05–0.15 mg/kg)[177,178] has been shown to be effective in the management of uric acid levels in adult patients with hyperuricemia or with high-risk factors for TLS. A recent phase II randomized trial compared the efficacy of rasburicase administered as a single dose (0.15 mg/kg, followed by additional days of dosing as needed) versus rasburicase (0.15 mg/kg/day) given for 5 days in adult patients at high risk or potential risk for TLS (N=80 treated).[179] The median pretreatment uric acid level was 8.5 mg/dL for high-risk patients (n=40) and 5.6 mg/dL for potential risk patients (n=40). Nearly all treated patients (99%) showed normalization of uric acid levels within 4 hours after the first dose of rasburicase; levels of uric acid were undetectable (<0.7 mg/dL) in 84% of patients.[179] In the single-dose rasburicase arm, 85% of patients had sustained uric acid response compared with 98% of patients in the 5-day rasburicase arm. Among high-risk patients within the single-dose arm, 6 patients received a second dose of rasburicase to achieve uric acid response.[179]

The risk factors for TLS include bone marrow involvement, bulky tumors that are chemosensitive, rapidly proliferative or aggressive hematologic malignancies, an elevated leukocyte count or

pretreatment LDH, pre-existing elevated uric acid, renal disease or renal involvement of tumor. Patients diagnosed with lymphoblastic lymphoma or Burkitt lymphoma are at a higher risk of developing TLS. Occasionally, patients with bulky presentation of DLBCL and patients with CLL and high white blood cell count may experience TLS at a moderately high frequency.

The NCCN Guidelines recommend that allopurinol be started 2−3 days prior to chemotherapy and continued for 10−14 days. Rasburicase is recommended for patients with any of the following risk factors: presence of any high risk feature (i.e., Burkitt lymphoma or lymphoblastic lymphomas; spontaneous TLS; elevated WBC count; elevated uric acid levels; bone marrow involvement; renal disease or renal involvement by tumor); bulky disease requiring immediate therapy; patients in whom adequate hydration is not possible; allopurinol is ineffective; or acute renal failure. A single dose is adequate in most cases; repeat dosing should be given on an individual basis.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9-29. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24399786.

2. Groves FD, Linet MS, Travis LB, Devesa SS. Cancer surveillance series: non-Hodgkin's lymphoma incidence by histologic subtype in the United States from 1978 through 1995. J Natl Cancer Inst 2000;92:1240-1251. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10922409.

3. Hicks EB, Rappaport H, Winter WJ. Follicular lymphoma; a re-evaluation of its position in the scheme of malignant lymphoma, based on a survey of 253 cases. Cancer 1956;9:792-821. Available at: http://www.ncbi.nlm.nih.gov/pubmed/13356265.

4. Rappaport H. Tumors of the hematopoietic system. In: Atlas of Tumor Pathology Series (ed I). Washington, DC: Armed Forces Institute of Pathology; 1966.

5. Bennetta MH, Farrer-Brown G, Henry K, et al. Classification of non-Hodgkin's lymphomas. Lancet 1974;2:405-408. Available at: http://www.ncbi.nlm.nih.gov/pubmed/4136882.

6. Lennert K. Malignant lymphomas other than Hodgkin's disease. New York: Springer-Verlag 1978.

7. Lennert K, Feller A. Histopathology of Non-Hodgkin's Lymphomas (ed 2nd Edition). Berlin: Springer-Verlag; 1992.

8. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: summary and description of a working formulation for clinical usage. The Non-Hodgkin's Lymphoma Pathologic Classification Project. Cancer 1982;49:2112-2135. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6896167.

9. Classification of non-Hodgkin's lymphomas. Reproducibility of major classification systems. NCI non-Hodgkin's Classification Project Writing Committee. Cancer 1985;55:91-95. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3965089.

10. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994;84:1361-1392. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8068936.

11. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 1997;89:3909-3918. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9166827.

12. Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. J Clin Oncol 1998;16:2780-2795. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9704731.

13. Harris NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. J Clin Oncol 1999;17:3835-3849. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10577857.

14. Jaffe ES, Harris. N.L., Stein H, Vardiman JW. WHO classification of tumours. Pathology and genetics of tumours of haematopoietic and lymphoid tissues Lyon: IARC; 2001.

15. Vose J, Armitage J, Weisenburger D. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol 2008;26:4124-4130. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18626005.

16. Jaffe ES, Harris NL, Stein H, Isaacson PG. Classification of lymphoid neoplasms: the microscope as a tool for disease discovery. Blood 2008;112:4384-4399. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19029456.

17. Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008.

18. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008;111:5446-5456. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18216293.

19. Rawstron AC, Bennett FL, O'Connor SJ, et al. Monoclonal B-cell lymphocytosis and chronic lymphocytic leukemia. N Engl J Med 2008;359:575-583. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18687638.

20. Hans CP, Weisenburger DD, Vose JM, et al. A significant diffuse component predicts for inferior survival in grade 3 follicular lymphoma, but cytologic subtypes do not predict survival. Blood 2003;101:2363-2367. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12424193.

21. Katzenberger T, Ott G, Klein T, et al. Cytogenetic alterations affecting BCL6 are predominantly found in follicular lymphomas grade 3B with a diffuse large B-cell component. Am J Pathol 2004;165:481-490. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15277222.

22. Lorsbach RB, Shay-Seymore D, Moore J, et al. Clinicopathologic analysis of follicular lymphoma occurring in children. Blood 2002;99:1959-1964. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11877266.

23. Harris NL, Swerdlow SH, Jaffe ES, et al. Follicular lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:220-226.

24. Oschlies I, Salaverria I, Mahn F, et al. Pediatric follicular lymphoma--a clinico-pathological study of a population-based series of patients treated within the Non-Hodgkin's Lymphoma--Berlin-Frankfurt-Munster (NHL-BFM) multicenter trials. Haematologica 2010;95:253-259. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19679882.

25. Louissaint A, Jr., Ackerman AM, Dias-Santagata D, et al. Pediatric-type nodal follicular lymphoma: an indolent clonal proliferation in children and adults with high proliferation index and no BCL2 rearrangement. Blood 2012;120:2395-2404. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22855608.

26. Liu Q, Salaverria I, Pittaluga S, et al. Follicular lymphomas in children and young adults: a comparison of the pediatric variant with usual follicular lymphoma. Am J Surg Pathol 2013;37:333-343. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23108024.

27. Cong P, Raffeld M, Teruya-Feldstein J, et al. In situ localization of follicular lymphoma: description and analysis by laser capture microdissection. Blood 2002;99:3376-3382. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11964306.

28. Sotomayor EA, Shah IM, Sanger WG, Mark HF. In situ follicular lymphoma with a 14;18 translocation diagnosed by a multimodal approach. Exp Mol Pathol 2007;83:254-258. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17482162.

29. Carbone A, Gloghini A, Santoro A. In situ follicular lymphoma: pathologic characteristics and diagnostic features. Hematol Oncol 2012;30:1-7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21560142.

30. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005;105:3768-3785. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15692063.

31. Hoefnagel JJ, Dijkman R, Basso K, et al. Distinct types of primary cutaneous large B-cell lymphoma identified by gene expression profiling. Blood 2005;105:3671-3678. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15308563.

32. Senff NJ, Hoefnagel JJ, Jansen PM, et al. Reclassification of 300 primary cutaneous B-Cell lymphomas according to the new WHO-EORTC classification for cutaneous lymphomas: comparison with previous classifications and identification of prognostic markers. J Clin Oncol 2007;25:1581-1587. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17353548.

33. Grange F, Bekkenk M, Wechsler J, et al. Prognostic factors in primary cutaneous large B-cell lymphomas: a European multicenter study. J Clin Oncol 2001;19:3602-3610. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11504742.

34. Willemze R, Meijer CJ, Sentis HJ, et al. Primary cutaneous large cell lymphomas of follicular center cell origin. A clinical follow-up study of nineteen patients. J Am Acad Dermatol 1987;16:518-526. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3546419.

35. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 2000;403:503-511. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10676951.

36. Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood 2004;103:275-282. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14504078.

37. Choi WWL, Weisenburger DD, Greiner TC, et al. A new immunostain algorithm classifies diffuse large B-cell lymphoma into molecular subtypes with high accuracy. Clin Cancer Res 2009;15:5494-5502. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19706817.

38. Fu K, Weisenburger DD, Choi WWL, et al. Addition of rituximab to standard chemotherapy improves the survival of both the germinal center B-cell-like and non-germinal center B-cell-like subtypes of diffuse large B-cell lymphoma. J Clin Oncol 2008;26:4587-4594. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18662967.

39. Meyer PN, Fu K, Greiner TC, et al. Immunohistochemical methods for predicting cell of origin and survival in patients with diffuse large B-cell lymphoma treated with rituximab. J Clin Oncol 2011;29:200-207. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21135273.

40. Nyman H, Adde M, Karjalainen-Lindsberg ML, et al. Prognostic impact of immunohistochemically defined germinal center phenotype in diffuse large B-cell lymphoma patients treated with immunochemotherapy. Blood 2007;109:4930-4935. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17299093.

41. Ferry JA. Burkitt's lymphoma: clinicopathologic features and differential diagnosis. Oncologist 2006;11:375-383. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16614233.

42. Dave SS, Fu K, Wright GW, et al. Molecular diagnosis of Burkitt's lymphoma. N Engl J Med 2006;354:2431-2442. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16760443.

43. Hummel MI, Bentink S, Berger H, et al. A biologic definition of Burkitt's lymphoma from transcriptional and genomic profiling. N Engl J Med 2006;354:2419-2430. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16760442.

44. Macpherson N, Lesack D, Klasa R, et al. Small noncleaved, non-Burkitt's (Burkitt-Like) lymphoma: cytogenetics predict outcome and reflect clinical presentation. J Clin Oncol 1999;17:1558-1567. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10334544.

45. Rosenwald A, Wright G, Leroy K, et al. Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to Hodgkin

lymphoma. J Exp Med 2003;198:851-862. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/12975453.

46. Traverse-Glehen A, Pittaluga S, Gaulard P, et al. Mediastinal gray zone lymphoma: the missing link between classic Hodgkin's lymphoma and mediastinal large B-cell lymphoma. Am J Surg Pathol 2005;29:1411-1421. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/16224207.

47. Hoefnagel JJ, Mulder MMS, Dreef E, et al. Expression of B-cell transcription factors in primary cutaneous B-cell lymphoma. Mod Pathol 2006;19:1270-1276. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/16778825.

48. Kodama K, Massone C, Chott A, et al. Primary cutaneous large B-cell lymphomas: clinicopathologic features, classification, and prognostic factors in a large series of patients. Blood 2005;106:2491-2497. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/15947086.

49. Grange F, Beylot-Barry M, Courville P, et al. Primary cutaneous diffuse large B-cell lymphoma, leg type: clinicopathologic features and prognostic analysis in 60 cases. Arch Dermatol 2007;143:1144-1150. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17875875.

50. Zinzani PL, Quaglino P, Pimpinelli N, et al. Prognostic factors in primary cutaneous B-cell lymphoma: the Italian Study Group for Cutaneous Lymphomas. J Clin Oncol 2006;24:1376-1382. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16492713.

51. Falini B, Pileri S, Zinzani PL, et al. ALK+ lymphoma: clinico-pathological findings and outcome. Blood 1999;93:2697-2706. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10194450.

52. Gascoyne RD, Aoun P, Wu D, et al. Prognostic significance of anaplastic lymphoma kinase (ALK) protein expression in adults with anaplastic large cell lymphoma. Blood 1999;93:3913-3921. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10339500.

53. Savage KJ, Harris NL, Vose JM, et al. ALK- anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. Blood 2008;111:5496-5504. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/18385450.

54. Sibon D, Fournier M, Briere J, et al. Long-term outcome of adults with systemic anaplastic large-cell lymphoma treated within the Groupe d'Etude des Lymphomes de l'Adulte trials. J Clin Oncol 2012;30:3939-3946. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/23045585.

55. Cheson BD, Horning SJ, Coiffier B, et al. Report of an International Workshop to standardize response criteria for Non-Hodgkin's Lymphomas. J Clin Oncol 1999;17:1244-1253. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/10561185.

56. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579-586. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/17242396.

57. Hehn ST, Grogan TM, Miller TP. Utility of fine-needle aspiration as a diagnostic technique in lymphoma. J Clin Oncol 2004;22:3046-3052. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15284254.

58. Meda BA, Buss DH, Woodruff RD, et al. Diagnosis and subclassification of primary and recurrent lymphoma. The usefulness and limitations of combined fine-needle aspiration cytomorphology and flow cytometry. Am J Clin Pathol 2000;113:688-699. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/10800402.

59. Dong HY, Harris NL, Preffer FI, Pitman MB. Fine-needle aspiration biopsy in the diagnosis and classification of primary and recurrent lymphoma: a retrospective analysis of the utility of cytomorphology and flow cytometry. Mod Pathol 2001;14:472-481. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/11353059.

60. Jeffers MD, Milton J, Herriot R, McKean M. Fine needle aspiration cytology in the investigation on non-Hodgkin's lymphoma. J Clin Pathol 1998;51:189-196. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9659258.

61. Zeppa P, Marino G, Troncone G, et al. Fine-needle cytology and flow cytometry immunophenotyping and subclassification of non-Hodgkin lymphoma: a critical review of 307 cases with technical suggestions. Cancer 2004;102:55-65. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14968418.

62. Dunphy CH. Applications of flow cytometry and immunohistochemistry to diagnostic hematopathology. Arch Pathol Lab Med 2004;128:1004-1022. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15335254

63. Howell SJ, Shalet SM. Fertility preservation and management of gonadal failure associated with lymphoma therapy. Curr Oncol Rep 2002;4:443-452. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12162920.

64. Conlan MG, Bast M, Armitage JO, Weisenburger DD. Bone marrow involvement by non-Hodgkin's lymphoma: the clinical significance of morphologic discordance between the lymph node and bone marrow. Nebraska Lymphoma Study Group. J Clin Oncol 1990;8:1163-1172. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1694234.

65. Lim ST, Tao M, Cheung YB, et al. Can patients with early-stage diffuse large B-cell lymphoma be treated without bone marrow biopsy? Ann Oncol 2005;16:215-218. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15668272.

66. Kim YH, Willemze R, Pimpinelli N, et al. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110:479-484. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17339420.

67. Senff N, Kluin-Nelemans H, Willemze R. Results of bone marrow examination in 275 patients with histological features that suggest an indolent type of cutaneous B-cell lymphoma. Br J Haematol 2008;142:52-56. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18422781.

68. Juneja SK, Wolf MM, Cooper IA. Value of bilateral bone marrow biopsy specimens in non-Hodgkin's lymphoma. J Clin Pathol 1990;43:630-632. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2401730.

69. Seam P, Juweid ME, Cheson BD. The role of FDG-PET scans in patients with lymphoma. Blood 2007;110:3507-3516. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17709603.

70. Isasi CR, Lu P, Blaufox MD. A metaanalysis of 18F-2-deoxy-2-fluoro-D-glucose positron emission tomography in the staging and restaging of patients with lymphoma. Cancer 2005;104:1066-1074. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16047335.

71. Trotman J, Fournier M, Lamy T, et al. Positron emission tomography-computed tomography (PET-CT) after induction therapy is highly predictive of patient outcome in follicular lymphoma: analysis of PET-CT in a subset of PRIMA trial participants. J Clin Oncol 2011;29:3194-3200. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21747087.

72. Feeney J, Horwitz S, Gonen M, Schoder H. Characterization of T-cell lymphomas by FDG PET/CT. AJR Am J Roentgenol 2010;195:333-340. Available at: http://www.ncbi.nlm.nih.gov/entrez/20651187.

73. Hoffmann M, Kletter K, Becherer A, et al. 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) for staging and follow-up

of marginal zone B-cell lymphoma. Oncology 2003;64:336-340. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12759529.

74. Rodriguez-Vigil B, Gomez-Leon N, Pinilla I, et al. PET/CT in lymphoma: prospective study of enhanced full-dose PET/CT versus unenhanced low-dose PET/CT. J Nucl Med 2006;47:1643-1648. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17015900.

75. Schaefer NG, Hany TF, Taverna C, et al. Non-Hodgkin lymphoma and Hodgkin disease: coregistered FDG PET and CT at staging and restaging--do we need contrast-enhanced CT? Radiology 2004;232:823-829. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15273335.

76. Lau GK. Hepatitis B reactivation after chemotherapy: two decades of clinical research. Hepatol Int 2008;2:152-162. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19669300.

77. Liang R. How I treat and monitor viral hepatitis B infection in patients receiving intensive immunosuppressive therapies or undergoing hematopoietic stem cell transplantation. Blood 2009;113:3147-3153. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19144986.

78. Lok AS, Liang RH, Chiu EK, et al. Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Report of a prospective study. Gastroenterology 1991;100:182-188. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1983820.

79. Matsue K, Kimura S, Takanashi Y, et al. Reactivation of hepatitis B virus after rituximab-containing treatment in patients with CD20-positive B-cell lymphoma. Cancer 2010;116:4769-4776. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20597091.

80. Targhetta C, Cabras MG, Mamusa AM, et al. Hepatitis B virus-related liver disease in isolated anti-hepatitis B-core positive lymphoma patients receiving chemo- or chemo-immune therapy.

Haematologica 2008;93:951-952. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18515881.

81. Tsutsumi Y, Kawamura T, Saitoh S, et al. Hepatitis B virus reactivation in a case of non-Hodgkin's lymphoma treated with chemotherapy and rituximab: necessity of prophylaxis for hepatitis B virus reactivation in rituximab therapy. Leuk Lymphoma 2004;45:627-629. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15160930.

82. Yeo W, Chan PK, Zhong S, et al. Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: a prospective study of 626 patients with identification of risk factors. J Med Virol 2000;62:299-307. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11055239.

83. Yeo W, Chan PKS, Ho WM, et al. Lamivudine for the prevention of hepatitis B virus reactivation in hepatitis B s-antigen seropositive cancer patients undergoing cytotoxic chemotherapy. J Clin Oncol 2004;22:927-934. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14990649.

84. FDA Drug Safety Communication: Boxed Warning and new recommendations to decrease risk of hepatitis B reactivation with the immune-suppressing and anti-cancer drugs Arzerra (ofatumumab) and Rituxan (rituximab); September 25, 2013. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM369436.pdf.

85. Borentain P, Colson P, Coso D, et al. Clinical and virological factors associated with hepatitis B virus reactivation in HBsAg-negative and anti-HBc antibodies-positive patients undergoing chemotherapy and/or autologous stem cell transplantation for cancer. J Viral Hepat 2010;17:807-815. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20002298.

86. Evens AM, Jovanovic BD, Su YC, et al. Rituximab-associated hepatitis B virus (HBV) reactivation in lymphoproliferative diseases: meta-analysis and examination of FDA safety reports. Ann Oncol

2011;22:1170-1180. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/21115603.

87. Fukushima N, Mizuta T, Tanaka M, et al. Retrospective and prospective studies of hepatitis B virus reactivation in malignant lymphoma with occult HBV carrier. Ann Oncol 2009;20:2013-2017. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19561036.

88. Ji D, Cao J, Hong X, et al. Low incidence of hepatitis B virus reactivation during chemotherapy among diffuse large B-cell lymphoma patients who are HBsAg-negative/ HBcAb-positive: a multicenter retrospective study. Eur J Haematol 2010;85:243-250. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20491883.

89. Koo YX, Tan DS, Tan IB, et al. Hepatitis B virus reactivation and role of antiviral prophylaxis in lymphoma patients with past hepatitis B virus infection who are receiving chemoimmunotherapy. Cancer 2010;116:115-121. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19899164.

90. Lalazar G, Rund D, Shouval D. Screening, prevention and treatment of viral hepatitis B reactivation in patients with haematological malignancies. Br J Haematol 2007;136:699-712. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17338776.

91. Lau GK, Leung YH, Fong DY, et al. High hepatitis B virus (HBV) DNA viral load as the most important risk factor for HBV reactivation in patients positive for HBV surface antigen undergoing autologous hematopoietic cell transplantation. Blood 2002;99:2324-2330. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11895763.

92. Yeo W, Chan TC, Leung NW, et al. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. J Clin Oncol 2009;27:605-611. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19075267.

93. Brechot C, Degos F, Lugassy C, et al. Hepatitis B virus DNA in patients with chronic liver disease and negative tests for hepatitis B

surface antigen. N Engl J Med 1985;312:270-276. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2981408.

94. Dhedin N, Douvin C, Kuentz M, et al. Reverse seroconversion of hepatitis B after allogeneic bone marrow transplantation: a retrospective study of 37 patients with pretransplant anti-HBs and anti-HBc. Transplantation 1998;66:616-619. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9753342.

95. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology 2007;45:507-539. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17256718.

96. Lau GK, Yiu HH, Fong DY, et al. Early is superior to deferred preemptive lamivudine therapy for hepatitis B patients undergoing chemotherapy. Gastroenterology 2003;125:1742-1749. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14724827.

97. Rossi G, Pelizzari A, Motta M, Puoti M. Primary prophylaxis with lamivudine of hepatitis B virus reactivation in chronic HbsAg carriers with lymphoid malignancies treated with chemotherapy. Br J Haematol 2001;115:58-62. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11722410.

98. Tsutsumi Y, Tanaka J, Kawamura T, et al. Possible efficacy of lamivudine treatment to prevent hepatitis B virus reactivation due to rituximab therapy in a patient with non-Hodgkin's lymphoma. Ann Hematol 2004;83:58-60. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14513286.

99. Ziakas PD, Karsaliakos P, Mylonakis E. Effect of prophylactic lamivudine for chemotherapy-associated hepatitis B reactivation in lymphoma: a meta-analysis of published clinical trials and a decision tree addressing prolonged prophylaxis and maintenance. Haematologica 2009;94:998-1005. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19454492.

100. Huang H, Li XY, Li HR, et al. Preventing hepatitis B reactivation in HBsAg-positive patients with untreated diffuse large B-cell lymphoma with R-CHOP chemotherapy: A prospective study to compare entecavir and lamivudine. ASCO Meeting Abstracts 2013;31:8503. Available at: http://meeting.ascopubs.org/cgi/content/abstract/31/15_suppl/8503.

101. Huang YH, Hsiao LT, Hong YC, et al. Randomized controlled trial of entecavir prophylaxis for rituximab-associated hepatitis B virus reactivation in patients with lymphoma and resolved hepatitis B. J Clin Oncol 2013;31:2765-2772. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23775967.

102. Kim SJ, Hsu C, Song YQ, et al. Hepatitis B virus reactivation in B-cell lymphoma patients treated with rituximab: analysis from the Asia Lymphoma Study Group. Eur J Cancer 2013;49:3486-3496. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23910494.

103. Allen MI, Deslauriers M, Andrews CW, et al. Identification and characterization of mutations in hepatitis B virus resistant to lamivudine. Lamivudine Clinical Investigation Group. Hepatology 1998;27:1670-1677. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9620341.

104. Gauthier J, Bourne EJ, Lutz MW, et al. Quantitation of hepatitis B viremia and emergence of YMDD variants in patients with chronic hepatitis B treated with lamivudine. J Infect Dis 1999;180:1757-1762. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10558928.

105. Law JK, Ali JA, Harrigan PR, et al. Fatal postlymphoma chemotherapy hepatitis B reactivation secondary to the emergence of a YMDD mutant strain with lamivudine resistance in a noncirrhotic patient. Am J Hematol 2006;81:969-972. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16937392.

106. Picardi M, Pane F, Quintarelli C, et al. Hepatitis B virus reactivation after fludarabine-based regimens for indolent non-Hodgkin's lymphomas: high prevalence of acquired viral genomic mutations.

Haematologica 2003;88:1296-1303. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14607759.

107. Schnepf N, Sellier P, Bendenoun M, et al. Reactivation of lamivudine-resistant occult hepatitis B in an HIV-infected patient undergoing cytotoxic chemotherapy. J Clin Virol 2007;39:48-50. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17368969.

108. Cortelezzi A, Vigano M, Zilioli VR, et al. Adefovir added to lamivudine for hepatitis B recurrent infection in refractory B-cell chronic lymphocytic leukemia on prolonged therapy with Campath-1H. J Clin Virol 2006;35:467-469. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16316778.

109. Peters MG, Hann Hw H, Martin P, et al. Adefovir dipivoxil alone or in combination with lamivudine in patients with lamivudine-resistant chronic hepatitis B. Gastroenterology 2004;126:91-101. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14699491.

110. Marcellin P, Heathcote EJ, Buti M, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Engl J Med 2008;359:2442-2455. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19052126.

111. Chan HL, Heathcote EJ, Marcellin P, et al. Treatment of hepatitis B e antigen positive chronic hepatitis with telbivudine or adefovir: a randomized trial. Ann Intern Med 2007;147:745-754. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17909201.

112. Leung N, Peng C-Y, Hann H-W, et al. Early hepatitis B virus DNA reduction in hepatitis B e antigen-positive patients with chronic hepatitis B: A randomized international study of entecavir versus adefovir. Hepatology 2009;49:72-79. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19065670.

113. Arnold DM, Crowther MA, Meyer RM, et al. Misleading hepatitis B test results due to intravenous immunoglobulin administration: implications for a clinical trial of rituximab in immune thrombocytopenia.

Transfusion 2010;50:2577-2581. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/20576011.

114. Arcaini L, Burcheri S, Rossi A, et al. Prevalence of HCV infection in nongastric marginal zone B-cell lymphoma of MALT. Ann Oncol 2007;18:346-350. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/17071937.

115. Arcaini L, Merli M, Volpetti S, et al. Indolent B-cell lymphomas associated with HCV infection: clinical and virological features and role of antiviral therapy. Clin Dev Immunol 2012;2012:638185. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/22956970.

116. de Sanjose S, Benavente Y, Vajdic CM, et al. Hepatitis C and non-Hodgkin lymphoma among 4784 cases and 6269 controls from the International Lymphoma Epidemiology Consortium. Clin Gastroenterol Hepatol 2008;6:451-458. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/18387498.

117. Engels EA, Chatterjee N, Cerhan JR, et al. Hepatitis C virus infection and non-Hodgkin lymphoma: results of the NCI-SEER multi-center case-control study. Int J Cancer 2004;111:76-80. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15185346.

118. Gisbert JP, Garcia-Buey L, Pajares JM, Moreno-Otero R. Prevalence of hepatitis C virus infection in B-cell non-Hodgkin's lymphoma: systematic review and meta-analysis. Gastroenterology 2003;125:1723-1732. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/14724825.

119. Mele A, Pulsoni A, Bianco E, et al. Hepatitis C virus and B-cell non-Hodgkin lymphomas: an Italian multicenter case-control study. Blood 2003;102:996-999. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/12714514.

120. Nieters A, Kallinowski B, Brennan P, et al. Hepatitis C and risk of lymphoma: results of the European multicenter case-control study

EPILYMPH. Gastroenterology 2006;131:1879-1886. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/17087949.

121. Schollkopf C, Smedby KE, Hjalgrim H, et al. Hepatitis C infection and risk of malignant lymphoma. Int J Cancer 2008;122:1885-1890. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18271005.

122. Spinelli JJ, Lai AS, Krajden M, et al. Hepatitis C virus and risk of non-Hodgkin lymphoma in British Columbia, Canada. Int J Cancer 2008;122:630-633. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/17935132.

123. Kawamura Y, Ikeda K, Arase Y, et al. Viral elimination reduces incidence of malignant lymphoma in patients with hepatitis C. Am J Med 2007;120:1034-1041. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/18060923.

124. Hermine O, Lefrere F, Bronowicki JP, et al. Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection. N Engl J Med 2002;347:89-94. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/12110736.

125. Kelaidi C, Rollot F, Park S, et al. Response to antiviral treatment in hepatitis C virus-associated marginal zone lymphomas. Leukemia 2004;18:1711-1716. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/15284859.

126. Tursi A, Brandimarte G, Torello M. Disappearance of gastric mucosa-associated lymphoid tissue in hepatitis C virus-positive patients after anti-hepatitis C virus therapy. J Clin Gastroenterol 2004;38:360-363. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/15087696.

127. Gisbert JP, Garcia-Buey L, Pajares JM, Moreno-Otero R. Systematic review: regression of lymphoproliferative disorders after treatment for hepatitis C infection. Aliment Pharmacol Ther 2005;21:653-662. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/15771751.

128. Vallisa D, Bernuzzi P, Arcaini L, et al. Role of anti-hepatitis C virus (HCV) treatment in HCV-related, low-grade, B-cell, non-Hodgkin's lymphoma: a multicenter Italian experience. J Clin Oncol 2005;23:468-473. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15659492.

129. La Mura V, De Renzo A, Perna F, et al. Antiviral therapy after complete response to chemotherapy could be efficacious in HCV-positive non-Hodgkin's lymphoma. J Hepatol 2008;49:557-563. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18678434.

130. Arcaini L, Vallisa D, Merli M, et al. Hematolgical response to antiviral treatment in 94 patients with indolent B-cell lymphomas associated with hepatitis C virus infection: a study of the Fondazione Italiana Linfomi (FIL) [abstract]. Ann Oncol 2011;22 (Suppl 4):Abstract 138. Available at: http://annonc.oxfordjournals.org/content/22/suppl_4/iv128.

131. Pellicelli AM, Marignani M, Zoli V, et al. Hepatitis C virus-related B cell subtypes in non Hodgkin's lymphoma. World J Hepatol 2011;3:278-284. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22125661.

132. Besson C, Canioni D, Lepage E, et al. Characteristics and outcome of diffuse large B-cell lymphoma in hepatitis C virus-positive patients in LNH 93 and LNH 98 Groupe d'Etude des Lymphomes de l'Adulte programs. J Clin Oncol 2006;24:953-960. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16418500.

133. Ennishi D, Maeda Y, Niitsu N, et al. Hepatic toxicity and prognosis in hepatitis C virus-infected patients with diffuse large B-cell lymphoma treated with rituximab-containing chemotherapy regimens: a Japanese multicenter analysis. Blood 2010;116:5119-5125. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20823454.

134. Nishikawa H, Tsudo M, Osaki Y. Clinical outcome in diffuse large B-cell lymphoma with hepatitis C virus infection in the rituximab era: a single center experience. Oncol Rep 2012;28:835-840. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22736295.

135. Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1207-1217. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21449784.

136. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011;364:2405-2416. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21696307.

137. McHutchison JG, Everson GT, Gordon SC, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. N Engl J Med 2009;360:1827-1838. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19403902.

138. Poordad F, McCone J, Jr., Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1195-1206. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21449783.

139. Ghany MG, Nelson DR, Strader DB, et al. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology 2011;54:1433-1444. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21898493.

140. Laurenti L, Piccioni P, Cattani P, et al. Cytomegalovirus reactivation during alemtuzumab therapy for chronic lymphocytic leukemia: incidence and treatment with oral ganciclovir. Haematologica 2004;89:1248-1252. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15477211.

141. Moreton P, Kennedy B, Lucas G, et al. Eradication of minimal residual disease in B-cell chronic lymphocytic leukemia after alemtuzumab therapy is associated with prolonged survival. J Clin

Oncol 2005;23:2971-2979. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/15738539.

142. Nguyen DD, Cao TM, Dugan K, et al. Cytomegalovirus viremia during Campath-1H therapy for relapsed and refractory chronic lymphocytic leukemia and prolymphocytic leukemia. Clin Lymphoma 2002;3:105-110. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/12435283.

143. O'Brien S, Ravandi F, Riehl T, et al. Valganciclovir prevents cytomegalovirus reactivation in patients receiving alemtuzumab-based therapy. Blood 2008;111:1816-1819. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/18039954.

144. Fiegl M, Falkner A, Hopfinger G, et al. Routine clinical use of alemtuzumab in patients with heavily pretreated B-cell chronic lymphocytic leukemia: a nation-wide retrospective study in Austria. Cancer 2006;107:2408-2416. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/17054106.

145. Hillmen P, Skotnicki AB, Robak T, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. J Clin Oncol 2007;25:5616-5623. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/17984186.

146. Keating MJ, Flinn I, Jain V, et al. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study. Blood 2002;99:3554-3561. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/11986207.

147. Lundin J, Kimby E, Bjorkholm M, et al. Phase II trial of subcutaneous anti-CD52 monoclonal antibody alemtuzumab (Campath-1H) as first-line treatment for patients with B-cell chronic lymphocytic leukemia (B-CLL). Blood 2002;100:768-773. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/12130484.

148. Stilgenbauer S, Zenz T, Winkler D, et al. Subcutaneous alemtuzumab in fludarabine-refractory chronic lymphocytic leukemia:

clinical results and prognostic marker analyses from the CLL2H study of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol 2009;27:3994-4001. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/19597025.

149. O'Brien SM, Keating MJ, Mocarski ES. Updated guidelines on the management of cytomegalovirus reactivation in patients with chronic lymphocytic leukemia treated with alemtuzumab. Clin Lymphoma Myeloma 2006;7:125-130. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/17026823.

150. Visani G, Mele A, Guiducci B, et al. An observational study of once weekly intravenous ganciclovir as CMV prophylaxis in heavily pre-treated chronic lymphocytic leukemia patients receiving subcutaneous alemtuzumab. Leuk Lymphoma 2006;47:2542-2546. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17169798.

151. Montillo M, Schinkoethe T, Elter T. Eradication of minimal residual disease with alemtuzumab in B-cell chronic lymphocytic leukemia (B-CLL) patients: the need for a standard method of detection and the potential impact of bone marrow clearance on disease outcome. Cancer Invest 2005;23:488-496. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/16203656.

152. Carson KR, Evens AM, Richey EA, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. Blood 2009;113:4834-4840. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/19264918.

153. FDA Prescribing Information for Rituxan® (rituximab). 2013. Available at:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/103705s5414lbl.pdf.

154. Hopfinger G, Plessl A, Grisold W, et al. Progressive multifocal leukoencephalopathy after rituximab in a patient with relapsed follicular lymphoma and low IgG levels and a low CD4+ lymphocyte count. Leuk

Lymphoma 2008;49:2367-2369. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/19052987.

155. Yokoyama H, Watanabe T, Maruyama D, et al. Progressive multifocal leukoencephalopathy in a patient with B-cell lymphoma during rituximab-containing chemotherapy: case report and review of the literature. Int J Hematol 2008;88:443-447. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/18855101.

156. Reddy N, Abel TW, Jagasia M, et al. Progressive multifocal leukoencephalopathy in a patient with follicular lymphoma treated with multiple courses of rituximab. Leuk Lymphoma 2009;50:460-462. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19266387.

157. D'Souza A, Wilson J, Mukherjee S, Jaiyesimi I. Progressive multifocal leukoencephalopathy in chronic lymphocytic leukemia: a report of three cases and review of the literature. Clin Lymphoma Myeloma Leuk 2010;10:E1-9. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/20223720.

158. Paues J, Vrethem M. Fatal progressive multifocal leukoencephalopathy in a patient with non-Hodgkin lymphoma treated with rituximab. J Clin Virol 2010;48:291-293. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/20558102.

159. Tuccori M, Focosi D, Blandizzi C, et al. Inclusion of rituximab in treatment protocols for non-Hodgkin's lymphomas and risk for progressive multifocal leukoencephalopathy. Oncologist 2010;15:1214-1219. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/21041380.

160. Tuccori M, Focosi D, Maggi F, et al. Progressive multifocal leukoencephalopathy: a report of three cases in HIV-negative patients with non-Hodgkin's lymphomas treated with rituximab. Ann Hematol 2010;89:519-522. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/19727726.

161. Chakraborty S, Tarantolo SR, Treves J, et al. Progressive Multifocal Leukoencephalopathy in a HIV-Negative Patient with Small Lymphocytic Leukemia following Treatment with Rituximab. Case Rep Oncol 2011;4:136-142. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/21691572.

162. Herold T, Seiler T, Egensperger R, et al. Progressive multifocal leukoencephalopathy after treatment with rituximab, fludarabine and cyclophosphamide in a patient with chronic lymphocytic leukemia. Leuk Lymphoma 2012;53:169-172. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/21812535.

163. Warsch S, Hosein PJ, Morris MI, et al. Progressive multifocal leukoencephalopathy following treatment with bendamustine and rituximab. Int J Hematol 2012;96:274-278. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/22684926.

164. Sikkema T, Schuiling WJ, Hoogendoorn M. Progressive multifocal leukoencephalopathy during treatment with rituximab and CHOP chemotherapy in a patient with a diffuse large B-cell lymphoma. BMJ Case Rep 2013;2013. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/23355583.

165. Arzerra (ofatumumab) Injection:Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER). September 2013. Available at:
http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm372685.htm.

166. FDA Drug Safety Communication: New Boxed Warning and Contraindication for Adcetris (brentuximab vedotin); January 13, 2012. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm287668.htm.

167. von Geldern G, Pardo CA, Calabresi PA, Newsome SD. PML-IRIS in a patient treated with brentuximab. Neurology 2012;79:2075-2077. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23115213.

168. Wagner-Johnston ND, Bartlett NL, Cashen A, Berger JR. Progressive multifocal leukoencephalopathy in a patient with Hodgkin lymphoma treated with brentuximab vedotin. Leuk Lymphoma 2012;53:2283-2286. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22424602.

169. Coiffier B, Altman A, Pui C, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol 2008;26:2767-2778. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18509186.

170. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol 2004;127:3-11. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15384972.

171. Krakoff IH, Meyer RL. Prevention of hyperuricemia in leukemia and lymphoma: use of allopurinol, a xanthine oxidase inhibitor. . JAMA 1965;193:1-6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14297704.

172. Bosly A, Sonet A, Pinkerton CR, et al. Rasburicase (recombinant urate oxidase) for the management of hyperuricemia in patients with cancer: report of an international compassionate use study. Cancer 2003;98:1048-1054. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12942574.

173. Coiffier B, Mounier N, Bologna S, et al. Efficacy and safety of rasburicase (recombinant urate oxidase) for the prevention and treatment of hyperuricemia during induction chemotherapy of aggressive non-Hodgkin's lymphoma: results of the GRAAL1 (Groupe d'Etude des Lymphomes de l'Adulte Trial on Rasburicase Activity in Adult Lymphoma) study. J Clin Oncol 2003;21:4402-4406. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14581437.

174. Cortes J, Moore JO, Maziarz RT, et al. Control of plasma uric acid in adults at risk for tumor lysis syndrome: efficacy and safety of rasburicase alone and rasburicase followed by allopurinol compared with allopurinol alone-results of a multicenter phase III study. J Clin

Oncol 2010;28:4207-4213. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20713865.

175. McDonnell AM, Lenz KL, Frei-Lahr DA, et al. Single-dose rasburicase 6 mg in the management of tumor lysis syndrome in adults. Pharmacotherapy 2006;26:806-812. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16716134.

176. Vines AN, Shanholtz CB, Thompson JL. Fixed-dose rasburicase 6 mg for hyperuricemia and tumor lysis syndrome in high-risk cancer patients. Ann Pharmacother 2010;44:1529-1537. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20841516.

177. Campara M, Shord SS, Haaf CM. Single-dose rasburicase for tumour lysis syndrome in adults: weight-based approach. J Clin Pharm Ther 2009;34:207-213. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19250141.

178. Knoebel RW, Lo M, Crank CW. Evaluation of a low, weight-based dose of rasburicase in adult patients for the treatment or prophylaxis of tumor lysis syndrome. J Oncol Pharm Pract 2011;17:147-154. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20332174.

179. Vadhan-Raj S, Fayad LE, Fanale MA, et al. A randomized trial of a single-dose rasburicase versus five-daily doses in patients at risk for tumor lysis syndrome. Ann Oncol 2012;23:1640-1645. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22015451.

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Follicular Lymphoma

Diagnosis

FL is the most common subtype of indolent NHL, and accounts for about 22% of all newly diagnosed cases of NHL.[1] About 90% of the cases have a t(14;18) translocation, which juxtaposes *BCL2* with the *IgH* locus resulting in the deregulated expression of BCL2.

Immunophenotyping using IHC and/or flow cytometry for cell surface marker analysis is required to establish a diagnosis. FL has a characteristic immunophenotype, which includes CD20+, CD10+, BCL2+, CD23+/-, CD43-, CD5-, CCND1- and BCL6+. Occasional cases of FL may be CD10- or BCL2-. The diagnosis is easily established on histological grounds, but immunophenotyping is encouraged to distinguish FL from a nodular MCL or SLL. Low-grade FL with a high proliferation index (as determined by Ki-67 immunostaining) has been shown to be associated with an aggressive clinical behavior. There is no evidence, however, that high Ki-67 should guide the selection of therapy.[2,3] Molecular genetic analysis to detect *BCL2* rearrangement, cytogenetics or FISH to identify t(14;18), and immunohistochemistry for Ki-67 may be useful under certain circumstances. In patients with BCL2-negative localized disease, the diagnosis of pediatric-type FL may be considered.

The Follicular Lymphoma International Prognostic Index (FLIPI) is a prognostic scoring system based on age, Ann Arbor stage, and number of nodal sites involved, hemoglobin levels and serum LDH levels.[4] The FLIPI was developed based on a large set of retrospective data from patients with FL, and established three distinct prognostic groups with 5-year survival outcomes ranging from 52.5% to 91% (in the pre-rituximab era).[4] In the National LymphoCare study, which analyzed the treatment options and outcomes of 2,728 patients with newly

diagnosed FL, FLIPI was able to categorize patients into three distinct prognostic groups.[5] In a more recent study conducted by the International Follicular Lymphoma Prognostic Factor Project, a prognostic model (FLIPI-2) was developed based on prospective collection of data from patients with newly diagnosed FL treated in the era of rituximab-containing chemoimmunotherapy regimens.[6] The final prognostic model included age, hemoglobin levels, longest diameter of largest involved lymph node, beta-2 microglobulin levels, and bone marrow involvement. FLIPI-2 was highly predictive of treatment outcomes, and separated patients into three distinct risk groups with 3-year progression-free survival (PFS) rates ranging from 51% to 91%, and OS rates ranging from 82% to 99%; the FLIPI-2 also defined distinct risk groups among the subgroup of patients treated with rituximab-containing regimens, with a PFS rate ranging from 57% to 89%.[6] Thus, FLIPI-2 may be useful for assessing prognosis in patients receiving active therapy with rituximab-based treatments. Both the FLIPI-1 and FLIPI-2 predict for prognosis, but these index scores have not yet been established as a means of selecting treatment options. Most recently, a simpler prognostic index incorporating only the baseline serum beta 2-microglobulin and LDH levels has been devised, which appears to be as predictive of outcomes as the FLIPI-1 and FLIPI-2 indices, and is easier to apply.[7,8]

In-situ Involvement of Follicular Lymphoma-like Cells of Unknown Significance (Follicular Lymphoma "in situ")

The presence of FL-like B-cells in the germinal centers of morphologically reactive lymph nodes (initially called "in situ localization of FL" or "follicular lymphoma in situ"[FLIS]) was first described a decade ago.[9,10] These cases are characterized by the preservation of the lymph node architecture, with the incidental finding of focal strongly

positive staining for BCL2 (restricted to germinal centers) and CD10 in the involved follicles, and the detection of t(14;18) by FISH. [9-12]

Cases of FLIS have been reported in patients with prior FL or concurrent FL (at other sites), as well as in individuals with no known history of FL.[9-11] The occurrence of FLIS in the general population appears to be rare. Based on data from a consecutive series of unselected surgical samples of reactive lymph nodes from patients (N=132; 1294 samples), the prevalence of FLIS was 2.3%.[13] Development of (or progression to) overt lymphoma in patients found to have FLIS has been reported, although this appears to be uncommon (5–6%).[14,15] The significance or potential for malignancy of FLIS in patients without known FL remains unclear. These cases may potentially represent the tissue counterpart of circulating B-cells with t(14;18), or may represent a very early lesion with t(14;18) but without other genetic abnormalities that lead to overt lymphoma.[10,14,16] The WHO classification recommends that a diagnosis of FL not be made in such cases, but that the report should suggest evaluation for the presence of FL elsewhere, and possibly close follow-up.

Pediatric-type Follicular Lymphoma

Pediatric-type FL is considered a rare variant of FL in the 2008 WHO classification,[10] and has been reported to comprise less than 2% of childhood NHLs.[17-20] In published studies, the median age at diagnosis of pediatric FL was approximately 11 years, and the large majority of cases were stage I or II at diagnosis with a predilection for localized nodal involvement in the head and neck region.[18-22] Histologically, pediatric FL cases tend to be associated with large expansive follicles with a "starry sky" pattern, high histologic grade (grade 3), and a high proliferation index.[20-22] Expression of BCL-2 protein may be observed in

approximately 40% to 50% of cases, and expression of Bcl-6 protein can be seen in the majority of cases.[19-22]

Importantly, the pediatric variant of FL is generally characterized by lack of *BCL2* rearrangement and t(14,18), which constitute the genetic hallmark of conventional FL cases seen in adults.[10,19-22] Rearrangement of *BCL6* is also typically absent in pediatric-type FL.[20,21] Expression of BCL-2 protein (by IHC) has been reported in approximately half of the cases of FL without *BCL2* rearrangement or t(14,18), as mentioned above.[20-22] Pediatric FL without *BCL2* rearrangements tend to be associated with localized disease with an indolent course and favorable prognosis, with only rare instances of disease progression or relapse.[19-22] In a recent analysis of FL cases in younger patients (age <40 years; n=27), a highly indolent pediatric-type FL was identified based on the lack of *BCL2* rearrangement concurrent with a high proliferation index (defined as ki-67 ≥ 30%).[21] These cases without *BCL2* rearrangement but with high proliferation index (n=21) were all stage I disease and none showed disease progression or relapse. In contrast, the remaining cases (n=6) with *BCL2* rearrangement and/or low proliferation index (defined as ki-67 <30%) all patients had stage III or IV disease, and 83% of these patients experienced disease progression or recurrence. Cases of indolent pediatric-type FL were also found among a separate cohort of adult patients; similar to the finding from the younger cohort of patients, adult patients without *BCL2* rearrangement but with high proliferation index (n=13) all had stage I disease, and none had progressed or relapsed after a median follow-up time of 61 months.[21] This study showed that pediatric-type FL characterized by lack of *BCL2* rearrangement, early-stage disease, and an indolent disease course can be diagnosed in adults. Cases of pediatric-type FL have primarily been managed with chemotherapy (with or without RT), excision only (with or without RT),

and more recently, chemoimmunotherapy with generally favorable outcomes and prognosis.[19,21,23]

Workup

The diagnostic workup for FL is similar to the workup for other lymphomas. The initial workup for newly diagnosed patients should include a thorough physical examination with attention to node-bearing areas, and evaluation of performance status and constitutional symptoms. Laboratory assessments should include CBC with differential and a comprehensive metabolic panel, in addition to measurements of serum lactate dehydrogenase (LDH) levels and serum beta-2 microglobulin. HBV testing is recommended due to increased risks of viral reactivation when chemoimmunotherapy regimens are being considered for treatment. Measurement of uric acid and hepatitis C testing may be useful for certain cases.

The majority of patients with FL will present with disseminated disease. The approach to therapy differs dramatically between patients with localized and those with disseminated disease. Bone marrow biopsy with aspirate is essential for documenting clinical stage I-II disease. Adequate trephine biopsy (specimen ≥1.6 cm)[24,25] should be obtained for initial staging evaluation, along with bone marrow aspiration. If radioimmunotherapy is considered, bilateral core biopsy is recommended; in such instances, the pathologist should provide the percent of overall cellular elements and the percent of cellular elements involved in the marrow. Bone marrow biopsy can be deferred if observation is the initial option.

The majority of the NCCN Member Institutions routinely employ chest, abdominal and pelvic CT as part of the diagnostic evaluation. CT scan of the neck may also assist in defining the extent of local disease. In patients presenting with what appears to be localized disease, a PET scan may be helpful in identifying occult sites of disease or if there is concern about histologic transformation.[26] PET does not replace histologic confirmation of the diagnosis; however, if there are sites with discordant high FDG-avidity, these represent the most likely sites of transformation. For patients being considered for treatment regimens containing anthracyclines or anthracenediones, a MUGA scan or echocardiogram should be obtained.

Treatment Options for Stage I-II FL

The NCCN Guidelines for FL apply to patients with grade FL1-2. Cases of FL3A and FL3B are commonly treated according to treatment recommendations for DLBCL.

Involved-site radiotherapy (ISRT) remains the current standard of care for patients with early-stage FL. Results from studies with long-term follow up showed favorable outcomes with RT in these patients.[27-30] In patients with stage I or II low-grade FL initially treated with involved- or extended-field RT, the median overall survival (OS) was about 14 years; 15-year OS rate was 40% and the 15-year relapse-free survival (RFS) or progression-free survival (PFS) was also about 40%.[29,30] In both of these studies, 41% of patients had stage I disease. The 15-year PFS outcomes were influenced by factors such as disease stage (66% for stage I vs. 26% for stage II disease) and maximal tumor size (49% for tumors < 3 cm vs. 29% for ≥ 3 cm). The OS rate was not significantly different between extended-field RT compared with IFRT (49% vs. 40%, respectively).[30] Long-term outcomes from another study of RT in patients with early-stage grade 1-2 FL (with or without chemotherapy) reported a median OS of 19 years and a 15-year OS rate of 62%.[28] In this study, the majority of patients (74%) had stage I disease and 24% had received chemotherapy with RT, which may have resulted in the higher OS rate reported compared with the aforementioned studies. In a

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recent study of patients with limited stage FL (grade 1 to 3A) treated with IFRT or reduced IFRT (RT of involved nodes only), the 10-year PFS and OS rates were 49% and 66%, respectively.[27] The reduction in radiation field size did not impact PFS or OS outcomes. Observation alone has been evaluated in patients with early-stage FL for whom toxicities related to IFRT were a concern. In a retrospective analysis of patients with stage I-II disease, carefully selected patients (requirement of large abdominal radiation field, advanced age, concern for xerostomia or patient refusal) who did not receive immediate treatment had comparable outcomes to those who were treated with RT.[31]

Sequential combination treatment with RT and chemotherapy has also been evaluated in patients with early-stage FL. In a prospective study of 44 patients with stage I-II low-grade NHL, the addition of cyclophosphamide, vincristine, prednisone, and bleomycin (COP-bleomycin) or CHOP-bleomycin to RT resulted in a 5-year failure-free survival (FFS) rate and OS rate of 74% and 89%, respectively.[32] The combination treatment appeared to improve failure-free survival but did not impact OS in patients with early-stage disease.[32] In a small prospective randomized study of RT alone compared with RT with adjuvant CHOP in patients with stage I low- or intermediate-grade NHL (n=44), the addition of adjuvant CHOP to RT did not improve relapse-free survival (RFS) or OS in the subgroup of patients with early-stage low-grade NHL.[33]

In a prospective analysis based on data from the National LymphoCare study registry, outcomes with different first-line management approaches were evaluated in the subgroup of patients (rigorously staged with bone marrow biopsy and complete imaging studies) with stage I FL (n=206).[34] First-line management strategies included observation only (i.e., "watch and wait") in 17%, RT only in 27%, rituximab monotherapy in 12%, rituximab combined with chemotherapy

(chemoimmunotherapy) in 28%, and combined modality with RT (typically involved chemoimmunotherapy prior to RT) in 13%. With a median follow up of 57 months, the median PFS with RT alone was 72 months; median PFS had not been reached with the other management approaches. After adjusting for tumor grade, LDH level and presence of B symptoms, treatment with chemoimmunotherapy or combined modality with RT improved PFS compared with RT alone (HRs of 0.36 and 0.11 respectively).[34] PFS outcomes did not differ between RT alone, observation alone and rituximab monotherapy. With the current follow up time, no differences in OS outcomes were observed between the various management approaches.[34] The study investigators suggested that the 'standard' approach of treating early-stage symptomatic FL with RT alone may be challenged in the current era of diverse therapeutic strategies.

A recent multicenter retrospective analysis evaluated outcomes in 145 patients with stage I or II FL who were managed with six different first-line treatment options (observation (i.e., "watchful waiting"), chemotherapy alone, RT alone, RT combined with chemotherapy, rituximab monotherapy and rituximab combined with chemotherapy (chemoimmunotherapy).[35] The median age was 55 years; 58% had stage I disease and 42% had stage II disease. Bulky disease was present in 15% of patients. For patients who received active therapy, the CR rates were 57% for single-agent rituximab, 69% for chemotherapy alone, 75% for chemoimmunotherapy, 81% for RT alone and 95% for RT combined with chemotherapy.[35] PFS rate at 7.5 years was highest with chemoimmunotherapy (60%) compared with other management options (19% with RT alone, 23% with chemotherapy alone, 26% with RT combined with chemotherapy and 26% for observation only; P =.00135). However, no significant differences were observed in OS at 7.5 years across the different approaches (66% with

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RT alone, 74% with chemotherapy alone, 67% with RT combined with chemotherapy, 72% with observation only, and 74% with chemoimmunotherapy).[35]

Treatment Options for Stage II (bulky) and Stage III-IV

Despite therapeutic advances that have improved outcomes, FL is generally considered a chronic disease characterized by multiple recurrences with current therapies. Several prospective randomized trials have failed to demonstrate a survival advantage with immediate treatment versus a "watch and wait" approach in patients with advanced stage, low tumor burden (or asymptomatic) FL.[36-38] These studies used chemotherapy regimens for the immediate treatment arm, as the studies were conducted prior to the standard incorporation of rituximab in FL therapy.

A randomized phase III intergroup trial evaluated the role of immediate treatment with rituximab (with or without additional rituximab maintenance) versus watchful waiting in patients with advanced stage, asymptomatic FL (n=462).[39] The primary endpoint of this trial was time to initiation of new therapy from randomization. Results from an interim analysis of this trial showed that immediate treatment with rituximab resulted in significantly longer median time to initiation of new therapy compared with observation alone (not reached at 4 years vs. 33 months; *P* <.001); median PFS was also significantly longer with rituximab compared with observation (not reached vs. approximately 24 months; *P* < .001). The endpoint chosen for this trial, however, is rather controversial considering that one arm of the trial involved initiation of early therapy; a more justifiable endpoint for this study could have been "time to initiation of second therapy". Moreover, no differences in OS were observed between the study arms.[39] Further follow up is needed to

evaluate whether immediate treatment with rituximab has an impact on time to second-line therapy.

In a more recent randomized phase III trial conducted by ECOG (E4402 study; RESORT), patients with low tumor burden FL (by GELF criteria) were treated with standard doses of rituximab, of which responding patients were then randomized to receive immediate maintenance with rituximab (n=140) or retreatment with rituximab upon progression (n=134).[40] The primary endpoint of this trial was time to treatment failure (TTF). Results from a planned interim analysis showed that at a median follow up of 3.8 years, median TTF was similar between the maintenance arm and retreatment arm (3.9 years vs. 3.6 years). Time to initiation of cytotoxic therapy was longer with maintenance rituximab compared with retreatment (95% vs. 86% remained free of cytotoxic therapy at 3 years), but both approaches delayed the initiation of cytotoxic therapy compared with historical "watch and wait" approaches in a similar population.[40] Evaluation of OS outcomes will require further follow up.

In a recent analysis based on data from the F2-study registry of the International Follicular Lymphoma Prognostic Factor Project, outcomes were evaluated in a cohort of patients with low-tumor burden FL who were initially managed by a "watch and wait" approach (n=107).[41] All of the patients in this cohort were asymptomatic, and 84% had stage III or IV disease. With a median follow up of 64 months, the median time observed without treatment was 55 months. Fifty-four patients (50%) required therapy, and among these patients, 71% received first-line treatment with rituximab-containing regimens. Multivariate analysis showed that involvement of more than 4 nodal areas was a significant independent predictor of shorter time to initiation of treatment. In order to assess whether an initial "watch and wait" approach would have negative effects on treatment efficacy during subsequent treatment,

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outcomes in this cohort were compared with those of patients from the F2-study registry who had low-tumor burden, asymptomatic FL, but were initially treated with rituximab-containing regimens (n=242).[41] The endpoint for the comparison was freedom from treatment failure (FFTF), which was defined as the time from diagnosis to one of the following events: progression during treatment, initiation of salvage therapy, relapse, or death from any cause. In the "watch and wait" cohort, initiation of first-line therapy was not considered an event for FFTF. The 4-year FFTF was 79% in the "watch and wait" cohort compared with 69% in the cohort initially treated with rituximab-containing regimens; the difference was not significant after adjusting for differences in baseline disease factors between the cohorts. In addition, the 5-year OS was similar (87% vs. 88%, respectively).[41] The investigators concluded that "watch and wait" remained a valid strategy even in the rituximab era, for the management of patients with prognostically favorable, low-tumor burden FL,

Collectively, findings from the above studies suggest that outside of clinical trials, observation is still the standard practice for patients with advanced stage low tumor burden FL. In the clinical practice setting, treatment should only be initiated when a patient presents with indications for treatment (based on GELF criteria).

Rituximab has demonstrated single-agent activity in previously untreated patients, as well in those with relapsed or refractory disease.[42-44] The addition of rituximab to combination chemotherapy regimens has consistently been associated with increased ORR, response duration and PFS outcomes.[45-49] In addition, some studies have demonstrated OS benefit with the addition of rituximab; a recent meta-analysis has confirmed the benefit in OS despite what is still limited follow up for FL.[50]

Long-term follow-up data from a multicenter phase II trial demonstrated the safety and efficacy of rituximab combined with CHOP chemotherapy (R-CHOP) in patients with relapsed or newly diagnosed indolent NHL.[46] The ORR rate was 100% with 87% of patients achieving a CR or CRu. The median time to progression and the duration of response was 82 months and 83.5 months respectively. The superiority of R-CHOP to CHOP as first-line therapy was established in a prospective randomized phase III study conducted by the German Low-Grade Lymphoma Study Group (GLSG) in previously untreated patients with advanced-stage FL (N=428). R-CHOP was associated with a 60% reduction in the relative risk for treatment failure, significantly prolonged time to treatment failure, higher ORR (but no difference in CR rate) and prolonged duration of remission.[47] OS analysis was complicated by a second randomization (for patients age <60 years), which included high-dose therapy followed by autologous stem cell rescue (HDT/ASCR). Outcomes were not significantly different with and without rituximab, in patients who received consolidation with HDT/ASCR. However, in patients who received interferon maintenance (who did not undergo HDT/ASCR), duration of remission was significantly improved with R-CHOP followed by interferon compared with CHOP/interferon (median not reached vs. 26 months). In addition, among the subgroup of older patients (age ≥60 years) who received interferon maintenance (as these patients were not eligible for HDT/ASCR), R-CHOP/interferon was associated with significantly improved 4-year PFS rate (62% vs. 28%) and OS rate (90% vs. 81%) compared with CHOP/interferon.[51]

In a randomized phase III study, addition of rituximab to CVP chemotherapy (R-CVP; n=162) compared with CVP (n=159) significantly improved outcome in patients with previously untreated FL, with no significant increase in toxicity.[48] At a median follow-up of

53 months, R-CVP was associated with improved ORR (81% vs. 57%), CR/CRu rate (41% vs. 10%), median time to progression (34 months vs. 15 months) and 4-year OS rate (83% vs. 77%).[49]

The addition of rituximab to fludarabine or fludarabine-based combination has also been evaluated in various clinical studies.[52-55] In a phase II study, rituximab combined with fludarabine (FR) was evaluated in patients with previously untreated or relapsed low-grade or follicular NHL (n=40; 68% previously untreated).[52] The ORR was 90% with 80% of patients achieving a CR. With a median follow-up time of 44 months, the median response duration, time to progression and OS had not been reached. The probability of OS at 50 months was estimated to be 80%. No significant differences in response or OS outcomes were noted between previously untreated and relapsed patients.[52] In a prospective randomized phase III trial (n=147; 128 evaluable patients), the combination of rituximab and FCM (fludarabine, cyclophosphamide, mitoxantrone; R-FCM) was associated with superior outcomes compared with FCM in patients with relapsed or refractory FL and MCL.[53] R-FCM resulted in significantly higher ORR (79% vs. 58%; *P*=0.01), higher CR rates (33% vs. 13%; *P* =.005), improved median PFS (16 months vs. 10 months; *P* =.038) and improved median OS (not reached at 3 years vs. 24 months; *P*=0.003) compared with FCM alone. In addition, among the subgroup of patients with FL (n=65), R-FCM was associated with significantly improved median PFS (not reached at 3 years vs. 21 months; *P* =.014); median OS (not reached in either treatment arm) was not significantly different.[53] In a randomized trial from the MD Anderson Cancer Center (MDACC), concurrent administration of rituximab with FND regimen (fludarabine, mitoxantrone and dexamethasone; R-FND) resulted in a significantly higher 3-year FFS rate (84% vs. 59% for sequential arm) in the subset of patients with FL.[54] In a subsequent report from the MDACC that

included an analysis of this study (concurrent or sequential inclusion of rituximab with FND) in patients with FL (n=151), the median FFS and OS had not been reached at a median follow up of 3.3 years; the 5-year FFS rate and OS rate with the regimen was 60% and 95%, respectively.[56] The combination of rituximab with fludarabine and mitoxantrone (R-FM) was evaluated in a phase II trial in patients with relapsed/refractory FL with high tumor burden (based on GELF criteria; n=50).[57] None of the patients were previously treated with rituximab, fludarabine or mitoxantrone. The ORR with this regimen was 84% (CR/CRu in 68%). The 3-year PFS rate and OS rate was 47% and 66%, respectively.[57]

The incorporation of rituximab to chemotherapy regimens has become a widely accepted standard of care for first-line therapy for patients with FL. However, no head-to-head randomized studies have shown superiority of one chemoimmunotherapy regimen over another with regards to OS outcomes. A report from the prospective, multicenter observational National LymphoCare Study based on the data collected from a large population of previously untreated patients with FL in the U.S. (n=2,738) showed that rituximab-containing chemoimmunotherapy was used in 52% of patients.[5] Among these patients, the most commonly employed regimens included R-CHOP (55%), R-CVP (23%) and rituximab with fludarabine-based regimens (R-Flu; 15.5%). In a recent analysis of patients treated with these rituximab-containing regimens in the National LymphoCare Study, 2-year PFS rates were similar between patients treated with R-CHOP, R-CVP or R-Flu (78% vs. 72% vs. 76%).[58] The 2-year OS rate showed significant differences, however (94% vs. 88% vs. 91%, respectively), with OS benefits observed for R-CHOP compared with R-CVP; this benefit with R-CHOP was more apparent in the subgroup of patients with poor-risk FLIPI scores.[58]

The phase III randomized trial of the Italian Lymphoma group (FOLL-05 Trial) evaluated the efficacy of three chemoimmunotherapy regimens (R-CVP, R-CHOP and R-FM) as first-line therapy in patients with advanced stage FL (n=534).[59] The primary endpoint of this study was time to treatment failure (TTF). The 3-year TTF rate was 46% for patients randomized to R-CVP, 62% for R-CHOP (*P* =.003 versus R-CVP) and 59% with R-FM (*P*=0.006 versus R-CVP), after a median follow up of 34 months. The 3-year PFS was 52%, 68%, and 63%, respectively (*P* =.011). No significant differences were observed between treatment arms for ORR or CR rates. The 3-year OS rate was 95% for all patients in this study.[59] Grade 3 or 4 neutropenia was more common in the R-FM arm, occurring in 64% of patients, compared with 28% with R-CVP and 50% with R-CHOP. The incidence of secondary malignancies was also more common with R-FM (8%) than with R-CVP (2%) or R-CHOP (3%).[59] Although these studies suggest a potential advantage of R-CHOP over R-CVP, both regimens are considered standard first-line therapies, and the selection of the optimal therapy would mainly depend on individual patient factors.

Fludarabine-based chemoimmunotherapy regimens may not be an ideal treatment option in the front-line setting because of the stem cell toxicity and increased risks for secondary malignancies associated with such regimens.[60-62] This may be of particular concern for younger patients with FL who may be candidates for autologous stem cell transplantation in the future. Prior exposure to fludarabine has been associated with poorer mobilization of peripheral blood stem cells in patients with lymphoma.[45,60-62]

Bendamustine, an alkylating agent with a purine-like benzimidazole ring component, has been shown to have low or incomplete cross-resistance with other alkylating agents due to its unique cytotoxic properties. Bendamustine (as a single agent or in combination with rituximab) has shown promising results with acceptable toxicity in patients with newly diagnosed as well as heavily pretreated relapsed or refractory indolent or mantle cell histologies or transformed NHL.[63-68] A multicenter randomized open-label phase III study conducted by the StiL (Study Group Indolent Lymphomas) compared rituximab combined with bendamustine (BR) with R-CHOP as first-line treatment in patients with advanced follicular, indolent, and mantle cell lymphomas (n=514).[69] The primary endpoint of this study was PFS, which was significantly longer with BR compared with R-CHOP (median 69.5 months vs. 31 months; hazard ratio=0.58, 95% CI 0.44–0.74; *P* <.0001). Median PFS was significantly longer with BR in the subgroup of patients with FL (n=279; not reached vs. 41 months; *P* =.0072). The ORR was similar between treatment arms (93% with BR; 91% with R-CHOP), although the CR rate was significantly higher in the BR arm (40% vs. 30%; *P*=.021).[69] With a median follow up of 45 months, no significant difference in OS was observed between treatment arms, and median OS has not been reached in either arm. The BR regimen was associated with a lower incidence of serious adverse events compared with R-CHOP (19% vs. 29%). In addition, BR was associated with less frequent grade 3 or 4 neutropenia (29% vs. 69%) or infections (any grade; 37% vs. 50%). Erythema (16% vs. 9%) and allergic skin reactions (15% vs. 6%) were more common with BR compared with R-CHOP. The incidence of secondary malignancies was similar, with 20 cases (8%) in the BR arm and 23 cases (9%) with R-CHOP.[69]

Another ongoing multicenter randomized open-label phase III study is evaluating the efficacy and safety of the BR regimen compared with R-CHOP/R-CVP in patients with previously untreated indolent NHL or mantle cell lymphoma (BRIGHT Study).[70] Among evaluable patients (N=419), the CR rate (assessed by an independent review committee) with BR was not inferior to R-CHOP/R-CVP (31% vs. 25%). The CR

rate in the subgroup of patients with indolent NHL was 27% and 23%, respectively. BR was associated with less grade 3 or 4 neutropenia (by laboratory assessment: 44% vs. 70%) but more infusion-related reactions (6% vs. 4%) compared with R-CHOP/R-CVP. Fatal adverse events occurred in 6 patients (3%) in the BR arm and 1 patient (<1%) in the R-CHOP/R-CVP arm.[70] In a phase II multicenter study, BR resulted in an ORR of 92% (CR in 41%) in patients with relapsed or refractory indolent and mantle cell lymphomas (N=67).[67] The median duration of response and PFS were 21 months and 23 months, respectively. Outcomes were similar for patients with indolent or mantle cell histologies.[67]

Bendamustine combined with rituximab and the proteasome inhibitor bortezomib (BVR) has been evaluated in two recent phase II studies in patients with relapsed and/or refractory FL.[63,64] In a study of 30 patients with relapsed/refractory indolent or mantle cell lymphoma (16 patients had FL; high-risk FLIPI, 56%; median 4 prior therapies), BVR regimen was associated with an ORR of 83% (CR in 52%).[64] The ORR was 93% among the subgroup of patients with FL and 75% for the subgroup with rituximab-refractory disease (n=10). The 2-year PFS rate was 47% and the median PFS for all patients was approximately 22 months. Serious adverse events were reported in 8 patients, which included 1 death due to sepsis.[64] In another study (VERTICAL) that evaluated a different BVR combination regimen in patients with relapsed/refractory FL (n=73; high-risk FLIPI, 38%; median 2 prior therapies), the ORR (among n=60 evaluable) was 88% (CR in 53%).[63] The median duration of response was 12 months. Among the subgroup of patients refractory to prior rituximab (n=20 evaluable), the ORR was 95%. The median PFS for all patients on the study was 15 months. Serious adverse events were reported in 34% of patients; the most common grade 3 or 4 adverse events were

myelotoxicities, fatigue, peripheral neuropathy, and gastrointestinal symptoms.[63]

The immunomodulating agent lenalidomide (a thalidomide analog indicated for the treatment of multiple myeloma and myelodysplastic syndromes), with or without rituximab, has also been evaluated in the treatment of both patients with previously untreated and relapsed/refractory indolent NHL. In a phase II trial of patients with relapsed/refractory indolent NHL (n=43; median 3 prior therapies), single-agent lenalidomide induced an ORR of 23% (CR /CRu in 7%).[71] Among the subgroup of patients with FL (n=22), the ORR was 27%. The median duration of response was longer than 16.5 months, and has not been reached. Median PFS for all patients was 4.4 months.[71] An ongoing randomized phase II trial is assessing the activity of lenalidomide alone compared with lenalidomide in combination with rituximab (CALGB 50401 study) in patients with recurrent FL (N=94; n=89 evaluable).[72] The ORR with lenalidomide alone was 49% (CR in 13%) and with the combination regimen was 75% (CR in 32%). With a median follow up of 1.5 years, median EFS was significantly longer with the combination (2 years vs. 1.2 years; *P*=.0063). Approximately 19% of patients in each arm discontinued therapy due to adverse events. Grade 3 or 4 adverse events were reported in a similar proportion of patients in the monotherapy and combination arms (49% vs. 52%; grade 4 in 9% in each arm). The most common grade 3 or 4 toxicities included neutropenia (16% vs. 19%), fatigue (9% vs. 14%), and thrombosis (16% vs. 4%).[72] The combination of lenalidomide and rituximab was also evaluated in a phase II study in patients with previously untreated indolent NHL (N=110; n=103 evaluable).[73] Among the subgroup of patients with FL (n=46), the ORR was 98% (CR/CRu in 87%) and the 2-year PFS was 89%. In patients with FL who had a positive PET scan prior to therapy (n=45), 93% achieved PET-negative response after treatment. Grade 3 or greater

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neutropenia was common, and occurred in 40% of patients overall. Thrombosis was reported in 3 patients (3%).[73]

Radioimmunotherapy (RIT) with the radio-labelled monoclonal antibodies ^{90}Y-ibritumomab tiuxetan[74-78] and ^{131}I-tositumumab[79-82] has been evaluated in patients with newly diagnosed, as well as those with relapsed, refractory or histologically transformed FL. In an international phase II trial, ^{90}Y-ibritumomab when used as a first-line therapy in older patients (age >50 years) with stage III or IV FL (N=59; median age 66 years, range 51–83 years) resulted in an ORR of 87% (CR in 41%, CRu in 15%) at 6 months after therapy.[78] After a median follow-up of approximately 31 months, the median PFS was 26 months and median OS has not been reached. The most common toxicities with first-line ^{90}Y-ibritumomab included grade 3 or 4 thrombocytopenia (48%; grade 4 in 7%) and neutropenia (32%; grade 4 in 17%). No grade 3 or 4 non-hematologic toxicities were reported. Grade 2 infections occurred in 20% and grade 2 GI toxicities in 10% of patients.[78] In a randomized phase III study in patients with relapsed or refractory low-grade, follicular or transformed lymphoma (n=143), ^{90}Y-ibritumomab tiuxetan also produced statistically and clinically significant higher ORR (80% vs. 56%) and CR rate (30% vs. 16%) compared with rituximab alone.[75] At a median follow-up of 44 months, median TTP (15 vs.10 months) and duration of response (17 vs. 11 months) were longer for patients treated with ^{90}Y-ibritumomab compared with rituximab.[76]

 Initial treatment with a single one-week course of ^{131}I-tositumomab induced prolonged clinical and molecular remissions in patients with advanced FL (N=76).[79] After a median follow-up of 10 years, the median duration of response was 6 years. For the 57 patients with a CR, median PFS was almost 11 years.[83] Ten-year PFS and OS rates were approximately 40% and 82%, respectively. Secondary

malignancies were reported in 11 patients (14%) during this long-term follow-up period, and 1 patient (1%) developed MDS about 8 years after therapy.[83] A single course of ^{131}I-tositumumab was significantly more efficacious than the last qualifying chemotherapy in extensively pretreated patients with refractory, low-grade, or transformed NHL (n=60).[81] The final results of the study demonstrated that ^{131}I-tositumumab resulted in long-term durable CRs. Among the 12 patients who achieved a CR, the median duration of response was nearly 10 years; among the 5 patients who continued in CR (lasting ≥10 years), none had received prior rituximab therapy.[84]

Phosphatidylinositol 3-kinase (PI3K) plays a central role in the normal B-cell development and function.[85] PI3Kδ signaling pathways are frequently hyperactive in B-cell neoplasms. Idelalisib, the isoform-selective oral inhibitor of PI3K-delta, has demonstrated promising clinical activity in phase I studies in patients with indolent NHL.[86] The safety and efficacy of idelalisib in patients with relapsed indolent NHL was evaluated in a phase II multicenter single arm study.[87] In this study, 122 patients with indolent NHL (72 patients with FL, 28 patients with SLL and 15 patients with MZL) that had not responded to previous treatment with rituximab and an alkylating agent were treated with idelalisib (150 mg oral, BID) until disease progression or patient withdrawal from the study.[87] Majority of the patients (89%) had stage III or IV disease. Among patients with FL, 79% of patients were of intermediate-risk or high-risk, based on FLIPI scores and 17% of patients had FL grade 3a. The primary end point of the study was the ORR. The median duration of treatment with idelalisib was 6.6 months. Idelalisib resulted in tumor reductions in 90% of the patients, with an ORR of 57% (6% CR and 50% PR). Response rates were similar across all subtypes of indolent NHL. The median duration of response, median PFS and OS were 12.5 months, 11.0 months and 20.3 months, respectively. At 48 weeks, 47% of the patients remained

progression-free. The median follow-up was 9.7 months. The most common adverse events of grade 3 or higher were neutropenia (27%), elevations in aminotransferase levels (13%), diarrhea (13%), and pneumonia (7%). Fatal and/or serious hepatotoxicity, severe diarrhea or colitis, pneumonitis, and intestinal perforation have been observed in patients treated with idelalisib.[88] See *"Special Considerations for the use of BCR Inhibitors"* in the guidelines for monitoring and management of adverse reactions associated with idelalisib.

Based on the results of this study, idelalisib (150 mg oral, BID) was recently approved by the FDA for the treatment of relapsed FL that has not responded to at least two prior systemic therapies. The NCCN Guidelines have included idelalisib as an option for second-line therapy for patients with relapsed or refractory FL.

First-line Consolidation with RIT
First-line chemotherapy followed by RIT with ^{90}Y-ibritumomab[89-92] or ^{131}I-tositumumab[93-96] has also been evaluated in several phase II studies.

In the international phase III trial (First-line Indolent Trial; FIT), patients with advanced stage FL responding to first-line induction therapy (n=414) were randomized to receive ^{90}Y-ibritumomab or no further treatment (observation only).[91] After a median follow-up of 7.3 years, the estimated 8-year PFS was 41% with ^{90}Y-ibritumomab tiuxetan consolidation and 22% with observation only, with a median PFS of 4.1 years versus 1.1 years, respectively ($P <.001$).[97] No significant difference in OS was observed between treatment arms. The incidence of secondary malignancies was higher in the consolidation arm compared with the observation arm (13% vs. 7%), but the difference was not statistically significant. MDS/AML occurred more frequently in the consolidation arm (3% vs. <1%), with a significantly increased

actuarial 8-year incidence rate (4.2% vs. 0.6%; $P <.042$). The median time from randomization to second malignancies was 58 months. The FIT study included only a small number of patients (14%) who received rituximab in combination with chemotherapy as induction.[91,97] Among these patients, the estimated 8-year PFS rate was 56% with ^{90}Y-ibritumomab consolidation and 45% with observation alone; the median PFS was greater than 7.9 years and 4.9 years, respectively. The difference in PFS outcomes was not significant in this subgroup; however, the trial was not statistically powered to detect differences in subgroups based on induction therapies.[97] Since only a small proportion of patients enrolled in the FIT trial received rituximab-containing induction therapy, the effects of RIT consolidation following rituximab-containing regimens cannot be fully evaluated.

In the Southwest Oncology Group (SWOG S9911) trial, CHOP followed by ^{131}I-tositumomab resulted in an ORR of 91%, including a 69% CR rate in patients with previously untreated, advanced FL (n=90).[95] After a median follow-up of 5 years, the estimated 5-year PFS rate and OS rate was 67% and 87%, respectively.[94] In a historical comparison, these results were more favorable than those reported for CHOP alone. In a multicenter phase II study, CVP chemotherapy followed by ^{131}I-tositumomab resulted in an ORR of 100% with a 93% CR rate in untreated patients with FL (n=30). The 5-year PFS rate and OS rate was 56% and 83%, respectively.[96]

The phase III randomized Intergroup study by the SWOG/CALGB (S0016) evaluated the role of RIT consolidation with ^{131}I-tositumumab (CHOP-RIT) following first-line therapy in patients with advanced stage FL.[7] In this study, 554 patients were randomized to first-line therapy with 6 cycles of R-CHOP or 6 cycles of CHOP followed by consolidation with ^{131}I-tositumumab (CHOP-RIT).[7] After a median follow-up time of 4.9 years, the estimated 2-year PFS (76% vs. 80%) and OS (97% vs. 93%)

rates were not significantly different between R-CHOP and CHOP-RIT. Median time to progression has not yet been reached for either study arm. Both the ORR (84% in each arm) and CR rates (40% vs. 45%, respectively) were also similar between treatment arms. CHOP-RIT was associated with a higher incidence of grade 3 or 4 thrombocytopenia (18% vs. 2%) but fewer febrile neutropenia (10% vs. 16%) compare with R-CHOP. The incidences of secondary malignancies (9% vs. 8%) and AML/MDS (1% vs. 3%) were not different between R-CHOP and CHOP-RIT.[7]

An ongoing trial (SWOG study S0801) is evaluating whether R-CHOP with RIT consolidation and with maintenance rituximab will provide improved efficacy outcomes. Data from this trial are awaited to assess the role of RIT consolidation in patients with FL treated with rituximab-containing induction.

First-line Consolidation with Maintenance Rituximab
Several studies have reported that prolonged administration of rituximab (or rituximab maintenance) significantly improved EFS in chemotherapy-naïve patients responding to initial rituximab induction, although this benefit did not translate to OS advantage.[98-100] In a study that evaluated maintenance rituximab compared with retreatment with rituximab upon progression in patients with chemotherapy-treated indolent lymphomas responsive to rituximab therapy (n=90 randomized), maintenance rituximab significantly improved PFS compared with the retreatment approach (31 months vs. 7 months; P=0.007).[101] However, retreatment with rituximab at progression provided the same duration of benefit from rituximab as did maintenance rituximab (31 months vs. 27 months).[101] Therefore, either approach (maintenance or retreatment at progression) appeared to be beneficial for this patient population. The randomized phase III study from ECOG (E1496) demonstrated a PFS benefit with rituximab

maintenance in patients with advanced indolent lymphoma responding to first-line chemotherapy with CVP (n=311; FL, n=282).[102] The 3-year PFS rate was 68% for maintenance rituximab compared with 33% for observation for all patients with advanced indolent lymphoma with response or stable disease after CVP chemotherapy. For the subgroup of patients with FL, the corresponding PFS rates were 64% and 33%, respectively; the 3-year OS rate was not significantly different in patients with FL (91% vs. 86%, respectively).[102]

The phase III randomized PRIMA trial prospectively evaluated the role of rituximab maintenance in patients responding to first-line chemotherapy in combination with rituximab.[103] In this study, patients with FL responding to first-line chemoimmunotherapy (R-CVP, R-CHOP or R-FCM) were randomized to observation only or rituximab maintenance for 2 years (n=1018). After a median follow-up of 36 months, the 3-year PFS rate was 75% in the rituximab maintenance arm and 58% in the observation arm (P =.0001). Two years after randomization, 71.5% of patients in the rituximab maintenance arm were in CR/CRu compared with 52% in the observation group.[103] However, no significant difference was observed in OS between the two groups. Based on multivariate analysis, induction therapy with R-CHOP or R-FCM was one of the independent factors associated with improved PFS, suggesting that R-CVP induction was not as beneficial in this study. Longer follow up is needed to evaluate the effect of rituximab maintenance on OS.

Second-line Consolidation with Maintenance Rituximab
Rituximab maintenance following second-line therapy has also been evaluated in patients with relapsed/refractory disease. Two large randomized trials have demonstrated a PFS advantage with rituximab maintenance over observation for patients treated with chemoimmunotherapy induction.[104-106] In a prospective phase III

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randomized study by the GLSG, rituximab maintenance after second-line treatment with R-FCM significantly prolonged duration of response in the subgroup of patients with recurring or refractory FL (n=81); median PFS with rituximab maintenance was not reached compared with 26 months in the observation arm (*P* =.035).[104] In a phase III randomized Intergroup trial (EORTC 20981) in patients with relapsed or resistant FL (n=334), responding to CHOP or R-CHOP induction therapy, maintenance rituximab significantly improved median PFS (3.7 years vs. 1.3 years; *P* <.001) compared with observation alone.[105,106] This PFS benefit was observed regardless of the induction therapy employed (CHOP or R-CHOP). With a median follow-up of 6 years, the 5-year OS rate was not significantly different between study arms (74% vs. 64%, respectively).[106]

Hematopoietic Stem Cell Transplantation (HSCT) After Induction

HDT/ASCR has been shown to prolong OS and PFS in patients with relapsed or refractory disease.[107-109] The GELA recently conducted a retrospective analysis of patients treated with chemotherapy alone in the first-line setting and found that EFS and survival after relapse were superior for patients treated with rituximab-containing regimens compared to chemotherapy only-based HDT/ASCR in relapsed or refractory FL.[110] The combination of rituximab-based second-line therapy followed by HDT/ASCR resulted in favorable survival rates after relapse, which was 90% at 5 years. Allogeneic HSCT is associated with high treatment-related mortality (TRM) rates (about 30-40% for myeloablative and 25% for nonmyeloablative allogeneic HSCT).[111,112] In a recent report from IBMTR, both myeloablative and nonmyeloablative HSCT resulted in similar TRM rates; however, nonmyeloablative allogeneic HSCT was associated with an increased risk of disease progression.[113]

Imaging Studies for FL

Imaging studies using CT or PET-CT scans are important components of diagnostic workup, interim restaging, and post-treatment assessments in patients with lymphomas. For patients with FL, CT scans of the chest, abdominal and pelvic regions are considered essential for diagnostic workup. The use of PET-CT is considered optional or useful in selected patients with FL during workup or for post-treatment assessment. Although PET-CT is now considered a standard part of post-treatment response evaluation in patients with aggressive NHLs or Hodgkin lymphoma, its role in patients with indolent lymphomas is less certain.

Several studies have reported on the potential usefulness of PET imaging in patients with indolent lymphomas, and documented the ability of this modality to detect lesions with high sensitivity (94–98%) and specificity (88–100%).[114-117] Studies have also suggested that PET/CT scans may be more accurate than CT scans alone in detecting disease.[116,118,119] In addition, post-treatment PET/CT scans have demonstrated prognostic utility in patients with indolent lymphomas. Several studies have shown that PET status (i.e., PET-positivity or PET-negativity at the end of induction therapy) was associated with PFS outcomes. In these studies, PET-negativity was associated with a longer PFS compared to PET-positivity.[114,119,120] In a retrospective study in patients with FL treated with R-CHOP, PET/CT imaging was found to be more accurate than CT imaging in detecting both nodal and extranodal lesions at staging and in assessing response to treatment.[120] Post-treatment PET/CT-negativity was associated with more favorable PFS outcomes; median PFS was 48 months among PET/CT-negative cases compared with 17 months for positive cases (*P* <.001).[120] An exploratory retrospective analysis of the prognostic value of post-induction PET/CT scans was conducted based on data obtained

from the PRIMA trial of patients with FL. In this trial, patients with previously untreated FL treated with rituximab-containing chemoimmunotherapy were randomized to rituximab maintenance (for 2 years) or observation only.[103] Among patients with a post-induction PET/CT scan (n=122), those with a positive PET/CT scan had a significantly inferior PFS rate compared with those who were PET negative (33% vs. 71% at 42 months; P <.001).[121] The median PFS was 20.5 months and not reached, respectively. Among the patients randomized to observation (n=57), PET/CT status remained significantly predictive of PFS outcomes. In this group, the 42-months PFS rate was 29% for PET/CT-positive patients compared with 68% in PET/CT-negative cases; median PFS was 30 months and 52 months, respectively.[103] Among the patients randomized to rituximab maintenance (n=47), PET/CT positivity was associated with inferior (but not statistically significant) PFS outcomes compared with PET/CT-negative cases (56% vs. 77% at 41 months); median PFS has not yet been reached in either the PET/CT-positive or PET/CT-negative subgroups. Moreover, PET/CT status was also associated with OS outcomes in this exploratory analysis. Patients who were PET/CT-positive after induction therapy had significantly inferior OS compared with PET/CT-negative patients (78.5% vs. 96.5% at 42 months; P =.001).[103]

In a recent prospective study, the prognostic value of PET imaging was evaluated in patients with high-tumor burden FL treated with first-line therapy with 6 cycles of R-CHOP (n=121; no maintenance rituximab administered).[122] PET scans were performed after 4 cycles of R-CHOP (interim PET) and at the end of treatment (final PET), and all scans were centrally reviewed. A positive PET was defined as Deauville score 4 or higher. Among patients with an interim PET scan (n=111), 76% had a PET-negative response. Among patients with a final PET (n=106),

78% had a PET-negative response.[122] At the end of treatment, nearly all patients (98%) who achieved a CR based on IWC also achieved a PET-negative response. Interim PET was associated with significantly higher 2-year PFS (86% for PET negative vs. 61% for positive; P=0.0046) but no significant difference in terms of OS. Final PET-negativity was associated with both significantly higher 2-year PFS (87% vs. 51%; P <.001) and higher OS (100% vs. 88%; P=0.013).[122] These studies suggest that post-treatment imaging studies may have a role as a predictive factor for survival outcomes in patients with FL. Further prospective studies are warranted to determine whether interim and/or end-of-treatment PET scans have a role in guiding post-induction therapeutic interventions.

PET scans may be useful in detecting transformation in patients with indolent NHL. Standard FDG uptake values (SUV) on PET have been reported to be higher among transformed than non-transformed cases of indolent lymphomas.[116] High SUVs on PET imaging should raise the suspicion of transformation to aggressive lymphoma, and can be used to direct the optimal site of biopsy for histological confirmation.[123]

Little data exist on the potential role of follow-up surveillance imaging for detection of relapse in patients with indolent NHL. In an early retrospective study, patients with stage I to stage III FL with a CR after induction were evaluated with clinical, laboratory and imaging studies during routine follow up (n=257).[124] Patients underwent CT scans of the abdomen and/or pelvis during follow-up visits. Follow up was typically performed every 3 to 6 months for the first 5 years of treatment, and then annually thereafter. The median follow-up time was 80 months (range, 13–209 months). Relapse was detected in 78 patients, with the majority of relapses (77%) occurring within the first 5 years of treatment.[124] Eleven of the relapses were detected with abdominal and/or pelvic CT scans alone. Thus, in this analysis, 4% of patients with

an initial CR had recurrence determined by routine surveillance with CT scans.[124] A more recent prospective study evaluated the role of surveillance PET scans in patients with lymphomas (Hodgkin lymphoma and NHL) with a CR after induction.[125] PET scans were performed every 6 months for the first 2 years after completion of induction, then annually thereafter. In the cohort of patients with indolent NHL (n=78), follow-up PET scans detected true relapses in 10% of patients (8 of 78) at 6 months, 12% (8 of 68) at 12 months, 9% (5 of 56) at 18 months, 9% (4 of 47) at 24 months, 8% (3 of 40) at 36 months and 6% (2 of 34) at 48 months.[125] Among 13 patients who were PET-positive without a corresponding abnormality on CT scan, relapse was documented in 8 of these patients by biopsy. Of the 47 patients with PET-positive relapses, 38 patients were detected on CT and 30 patients were detected clinically at the same time as the PET. It is unclear whether this earlier detection of relapse in a proportion of patients translates to improved outcomes.

In the absence of evidence demonstrating improved survival outcomes with early PET detection of relapse, PET scans are not recommended for routine surveillance in patients who have achieved a CR after treatment.

NCCN Recommendations for Treatment of Stage I-II Disease

Involved-site radiotherapy (ISRT; 24–30 Gy, with an additional 6 Gy in selected patients with bulky disease) is the preferred treatment option for patients with stage I or contiguous stage II disease. In selected cases where toxicity of ISRT outweighs the potential clinical benefit, observation may be appropriate. Alternate treatment options include immunotherapy with or without chemotherapy with or without RT. Because chemotherapy added to RT was not shown to provide

relapse-free survival benefit, chemotherapy plus RT is included in the NCCN Guidelines with a category 2B recommendation.

For patients with a PR following initial immunotherapy with or without chemotherapy (but without RT), additional treatment with ISRT should be considered. Otherwise, for patients with a clinical PR (following ISRT) or CR, clinical follow-up with a complete physical exam and laboratory assessment should be performed every 3 to 6 months for the first 5 years, and then annually (or as clinically indicated) thereafter. Surveillance imaging with CT scans can be performed no more than every 6 months up to the first 2 years following completion of treatment, and then no more than annually (or as clinically indicated) thereafter. Patients with no response to initial therapy should be managed in the same manner as patients with advanced disease, as described below.

NCCN Recommendations for Treatment of Stage II (bulky) and Stage III-IV Disease

As previously mentioned, treatment for patients with advanced-stage FL in the clinical practice setting should only be initiated when indicated by the GELF criteria. The modified criteria used to determine treatment initiation include: symptoms attributable to FL (not limited to B-symptoms); threatened end-organ function; cytopenia secondary to lymphoma; bulky disease (single mass >7 cm or 3 or more masses >3 cm), splenomegaly; and steady progression over at least 6 months. Treatment decisions should also consider the patient's preference; however, patients opting for immediate treatment in the absence of a clinical indication should be referred to an appropriate clinical trial. The selection of treatment should be highly individualized according to the patient's age, extent of disease, presence of comorbid conditions, and the goals of therapy. When choosing an initial therapy, care should be given to avoid excessively myelotoxic regimens in patients who may subsequently be candidates for HDT/ASCR. Chemoimmunotherapy

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regimens (containing rituximab) frequently used in the management of FL may be associated with risks for reactivation of HBV, which can lead to hepatitis and hepatic failure. Therefore, prior to initiation of therapy, HBV testing (including HBsAg and HBcAb testing) should be performed for all patients; viral load should be monitored routinely for patients with positive test results. In addition, the use of empiric antiviral therapy or upfront prophylaxis should be incorporated into the treatment plan.

First-line Therapy

In the absence of an appropriate clinical trial, patients with indications for treatment should be treated with systemic therapy. In selected cases such as the elderly frail patient who would not tolerate chemotherapy, ISRT (4 Gy) may be used for local palliation. Asymptomatic patients, especially those older than 70 years of age, should be observed.[38]

Based on the reported data, rituximab in combination with bendamustine, CHOP or CVP chemotherapy for first-line therapy in patients with advanced FL are all category 1 recommendations. In the absence of a randomized trial showing superior OS with R-CHOP versus R-CVP, either of these regimens can be considered appropriate in the first-line setting. The BR regimen has been shown to have less toxicity and a superior PFS compared to R-CHOP in a randomized phase III study; however, the OS outcomes were not significantly different. Furthermore, we have limited data on the risk of secondary MDS/AML after bendamustine. Data from a limited subset of patients suggests that peripheral blood stem cells can be collected after both BR and R-CHOP; additional data are needed to confirm this finding. Other suggested regimens include rituximab either as a single agent or in combination with fludarabine-based chemotherapy. As discussed earlier, the use of fludarabine-containing regimens may not

be ideal in the first-line setting for younger, physically fit patients (who may be candidates for future HDT/HSCR) because of the stem cell toxicity and risks for secondary malignancies. Thus, the use of regimens such as R-FND in the first-line setting is included as a category 2B recommendation. RIT is included as a category 3 option due to the absence of additional data from randomized studies. ISRT (4–30 Gy) with or without systemic therapy can be considered for palliation in patients with locally bulky or symptomatic disease if they are unable to tolerate systemic therapy.

Single-agent rituximab is the preferred first-line therapy for elderly or infirm patients. Single-agent cyclophosphamide had equivalent OS and CR rates compared to cyclophosphamide-based combination chemotherapy.[126] The NCCN Guidelines have also included RIT, alkylating agent-based chemotherapy (cyclophosphamide or chlorambucil) with or without rituximab, as alternative options for elderly or infirm patients.

First-line Consolidation or Extended Dosing

Patients with CR or PR to first-line therapy can either be observed or can be treated with optional consolidation or extended therapy. Based on the results of the PRIMA study,[103] maintenance therapy with rituximab (one dose every 8 weeks) up to 2 years is recommended (category 1) for patients responding to first-line chemoimmunotherapy. Based on the results of the FIT trial,[91,97] RIT is recommended (category 1) for patients who received first-line chemotherapy.

As of February 2014, [131I]-tositumumab has been discontinued and will no longer be available for the treatment of patients with FL.

For patients receiving consolidation therapy, clinical follow-up with a complete physical exam and laboratory assessment should be performed every 3 to 6 months for the first 5 years, and then annually

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(or as clinically indicated) thereafter. Surveillance imaging with CT scans can be performed no more than every 6 months up to the first 2 years following completion of treatment, and then no more than annually (or as clinically indicated) thereafter.

Second-line Therapy for Relapsed or Progressive Disease

Frequently, patients will benefit from a second period of observation after progressing from first-line therapy. Thus, treatment for relapsed or progressive disease is based on the modified GELF criteria as in first-line therapy. Progressive disease should be histologically documented to exclude transformation, especially in the presence of raising LDH levels, disproportional growth in one area, development of extranodal disease or development of new constitutional symptoms. Areas of high SUV, especially in values in excess of 13.1, should raise suspicion for the presence of transformation. However, a positive PET/CT scan does not replace a biopsy; rather, results of the PET/CT scan should be used to direct a biopsy to enhance the diagnostic yield from the biopsy. For patients requiring second-line therapy or treatment for disease unresponsive to first-line regimens, the options include chemoimmunotherapy regimens used for first-line treatment, BVR (bendamustine, bortezomib, rituximab), fludarabine combined with rituximab, FCM-R regimen (category 1) or RIT (category 1) or any of the second-line regimens used for patients with DLBCL. Based on the recent FDA approval, idelalisib is also included as an option for second-line therapy.

As of February 2014, [131I]-tositumumab has been discontinued and will no longer be available for the treatment of patients with FL.

Second-line Consolidation or Extended Dosing

For patients in remission after second-line therapy, optional maintenance therapy with rituximab (one dose every 12 weeks for 2 years) can be recommended (category 1). However, the NCCN Guidelines panel recognizes that the efficacy of maintenance rituximab in the second-line setting would likely be impacted by a patient's response to first-line maintenance with rituximab. If a patient progressed during or within 6 months of first-line maintenance with rituximab, the clinical benefit of maintenance in the second-line setting is likely very minimal. HDT/ASCR is an appropriate consolidative therapy for patients with second or third remission. Allogeneic HSCT may also be considered for highly selected patients. For patients receiving consolidation therapy, clinical follow-up with a complete physical exam and laboratory assessment should be performed every 3 to 6 months for the first 5 years, and then annually (or as clinically indicated) thereafter. Surveillance imaging with CT scans can be performed no more than every 6 months up to the first 2 years following completion of treatment, and then no more than annually (or as clinically indicated) thereafter.

Histological Transformation to DLBCL

In patients with FL, histological transformation to DLBCL is generally associated with a poor clinical outcome. Histological transformation to DLBCL occurs at an annual rate of approximately 3% for 15 years and the risk of transformation falls after that time, for reasons that remain unclear.[127] In a multivariate analysis, advanced stage disease at diagnosis was the only predictor of future transformation. The median OS after transformation has been reported to be less than 2 years.[127] However, patients with limited disease with no previous exposure to chemotherapy may have the favorable outcomes similar to *de novo* DLBCL.[128] The 5-year OS rate for patients with limited extent transformation was 66% compared with 19% for those with advanced disease (*P*<0.0001).[127]

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Non-Hodgkin's Lymphomas

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Discussion

In cases where the patient has had multiple prior therapies, the prognosis is much poorer and enrollment in an appropriate clinical trial is the preferred option. In the absence of a suitable clinical trial, treatment options include RIT, chemotherapy with or without rituximab, ISRT or best supportive care. HDT/ASCR or allogeneic HSCT can be considered as consolidation therapy for patients in remission after initial treatment. In a multicenter cohort study (172 patients) conducted by the Canadian blood and bone marrow transplant group, HDT/ASCR was associated with better outcomes than rituximab-based chemotherapy alone for patients aggressive histological transformation.[129] The 5-year OS after transformation was 65%, 61% and 46% respectively for patients treated with HDT/ASCR, rituximab-containing chemotherapy and allogeneic SCT. The corresponding 5-year PFS rates after transformation were 55%, 40% and 46% respectively.

If the patient has had minimal (ISRT alone or one course of single-agent therapy including rituximab) or no prior chemotherapy, anthracycline-based chemotherapy with rituximab, with or without RT is included as a treatment option. Enrollment in clinical trial is recommended for all patients following initial therapy. Patients responding to initial treatment (with a PR or CR) could also be considered for consolidation therapy with HDT/ASCR or allogeneic HSCT. Alternatively, patients with CR to initial therapy may be observed and RIT may be considered for those with PR. Patients with no response or progressive disease following initial therapy should be treated with RIT, palliative therapy or best supportive care.

References

1. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 1997;89:3909-3918. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9166827.

2. Koster A, Tromp HA, Raemaekers JM, et al. The prognostic significance of the intra-follicular tumor cell proliferative rate in follicular lymphoma. Haematologica 2007;92:184-190. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17296567.

3. Wang SA, Wang L, Hochberg EP, et al. Low histologic grade follicular lymphoma with high proliferation index: morphologic and clinical features. Am J Surg Pathol 2005;29:1490-1496. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16224216.

4. Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood 2004;104:1258-1265. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15126323.

5. Friedberg JW, Taylor MD, Cerhan JR, et al. Follicular lymphoma in the United States: first report of the national LymphoCare study. J Clin Oncol 2009;27:1202-1208. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19204203.

6. Federico M, Bellei M, Marcheselli L, et al. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. J Clin Oncol 2009;27:4555-4562. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19652063.

7. Press OW, Unger JM, Rimsza LM, et al. Phase III randomized intergroup trial of CHOP plus rituximab compared with CHOP chemotherapy plus (131)iodine-tositumomab for previously untreated follicular non-Hodgkin lymphoma: SWOG S0016. J Clin Oncol 2013;31:314-320. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23233710.

8. Press OW, Unger JM, Rimsza LM, et al. A comparative analysis of prognostic factor models for follicular lymphoma based on a phase III trial of CHOP-rituximab versus CHOP + 131iodine--tositumomab. Clin Cancer Res 2013;19:6624-6632. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24130072.

9. Cong P, Raffeld M, Teruya-Feldstein J, et al. In situ localization of follicular lymphoma: description and analysis by laser capture microdissection. Blood 2002;99:3376-3382. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11964306.

10. Harris NL, Swerdlow SH, Jaffe ES, et al. Follicular lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:220-226.

11. Sotomayor EA, Shah IM, Sanger WG, Mark HF. In situ follicular lymphoma with a 14;18 translocation diagnosed by a multimodal approach. Exp Mol Pathol 2007;83:254-258. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17482162.

12. Carbone A, Gloghini A, Santoro A. In situ follicular lymphoma: pathologic characteristics and diagnostic features. Hematol Oncol 2012;30:1-7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21560142.

13. Henopp T, Quintanilla-Martinez L, Fend F, Adam P. Prevalence of follicular lymphoma in situ in consecutively analysed reactive lymph nodes. Histopathology 2011;59:139-142. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21771030.

14. Jegalian AG, Eberle FC, Pack SD, et al. Follicular lymphoma in situ: clinical implications and comparisons with partial involvement by follicular lymphoma. Blood 2011;118:2976-2984. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21768298.

15. Pillai RK, Surti U, Swerdlow SH. Follicular lymphoma-like B-cells of uncertain significance (in situ follicular lymphoma) may infrequently

progress, but precedes follicular lymphoma, is associated with other overt lymphomas and mimics follicular lymphoma in flow cytometric studies. Haematologica 2013;98:1571-1580. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23831923.

16. Bonzheim I, Salaverria I, Haake A, et al. A unique case of follicular lymphoma provides insights to the clonal evolution from follicular lymphoma in situ to manifest follicular lymphoma. Blood 2011;118:3442-3444. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21940830.

17. Frizzera G, Murphy SB. Follicular (nodular) lymphoma in childhood: a rare clinical-pathological entity. Report of eight cases from four cancer centers. Cancer 1979;44:2218-2235. Available at: http://www.ncbi.nlm.nih.gov/pubmed/389411.

18. Ribeiro RC, Pui CH, Murphy SB, et al. Childhood malignant non-Hodgkin lymphomas of uncommon histology. Leukemia 1992;6:761-765. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1640726.

19. Lorsbach RB, Shay-Seymore D, Moore J, et al. Clinicopathologic analysis of follicular lymphoma occurring in children. Blood 2002;99:1959-1964. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11877266.

20. Oschlies I, Salaverria I, Mahn F, et al. Pediatric follicular lymphoma--a clinico-pathological study of a population-based series of patients treated within the Non-Hodgkin's Lymphoma--Berlin-Frankfurt-Munster (NHL-BFM) multicenter trials. Haematologica 2010;95:253-259. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19679882.

21. Louissaint A, Jr., Ackerman AM, Dias-Santagata D, et al. Pediatric-type nodal follicular lymphoma: an indolent clonal proliferation in children and adults with high proliferation index and no BCL2 rearrangement. Blood 2012;120:2395-2404. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22855608.

22. Liu Q, Salaverria I, Pittaluga S, et al. Follicular lymphomas in children and young adults: a comparison of the pediatric variant with usual follicular lymphoma. Am J Surg Pathol 2013;37:333-343. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23108024.

23. Kumar R, Galardy PJ, Dogan A, et al. Rituximab in combination with multiagent chemotherapy for pediatric follicular lymphoma. Pediatr Blood Cancer 2011;57:317-320. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21462303.

24. Bain BJ. Bone marrow trephine biopsy. J Clin Pathol 2001;54:737-742. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11577117.

25. Bishop PW, McNally K, Harris M. Audit of bone marrow trephines. J Clin Pathol 1992;45:1105-1108. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1479037.

26. Schoder H, Noy A, Gonen M, et al. Intensity of 18fluorodeoxyglucose uptake in positron emission tomography distinguishes between indolent and aggressive non-Hodgkin's lymphoma. J Clin Oncol 2005;23:4643-4651. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15837966.

27. Campbell BA, Voss N, Woods R, et al. Long-term outcomes for patients with limited stage follicular lymphoma: involved regional radiotherapy versus involved node radiotherapy. Cancer 2010;116:3797-3806. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20564082.

28. Guadagnolo BA, Li S, Neuberg D, et al. Long-term outcome and mortality trends in early-stage, Grade 1-2 follicular lymphoma treated with radiation therapy. Int J Radiat Oncol Biol Phys 2006;64:928-934. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16243446.

29. Mac Manus MP, Hoppe RT. Is radiotherapy curative for stage I and II low-grade follicular lymphoma? Results of a long-term follow-up study of patients treated at Stanford University. J Clin Oncol 1996;14:1282-1290. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8648385.

30. Wilder RB, Jones D, Tucker SL, et al. Long-term results with radiotherapy for Stage I-II follicular lymphomas. Int J Radiat Oncol Biol Phys 2001;51:1219-1227. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11728680.

31. Advani R, Rosenberg S, Horning S. Stage I and II follicular non-Hodgkin's lymphoma: long-term follow-up of no initial therapy. J Clin Oncol 2004;22:1454-1459. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15024027.

32. McLaughlin P, Fuller L, Redman J, et al. Stage I-II low-grade lymphomas: a prospective trial of combination chemotherapy and radiotherapy. Ann Oncol 1991;2 Suppl 2:137-140. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1710918.

33. Yahalom J, Varsos G, Fuks Z, et al. Adjuvant cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy after radiation therapy in stage I low-grade and intermediate-grade non-Hodgkin lymphoma. Results of a prospective randomized study. Cancer 1993;71:2342-2350. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8453557.

34. Friedberg JW, Byrtek M, Link BK, et al. Effectiveness of first-line management strategies for stage I follicular lymphoma: analysis of the National LymphoCare Study. J Clin Oncol 2012;30:3368-3375. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22915662.

35. Michallet AS, Lebras LL, Bauwens DD, et al. Early stage follicular lymphoma: what is the clinical impact of the first-line treatment strategy? J Hematol Oncol 2013;6:45. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23816219.

36. Young RC, Longo DL, Glatstein E, et al. The treatment of indolent lymphomas: watchful waiting v aggressive combined modality treatment. Semin Hematol 1988;25:11-16. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2456618.

37. Brice P, Bastion Y, Lepage E, et al. Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 1997;15:1110-1117. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9060552.

38. Ardeshna KM, Smith P, Norton A, et al. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. Lancet 2003;362:516-522. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12932382.

39. Ardeshna K, Qian W, Smith P, et al. An Intergroup randomized trial of rituximab versus a watch and wait strategy in patients with stage II, III, IV, asymptomatic, non-bulky follicular lymphoma (grades 1, 2 and 3a). A preliminary analysis [abstract] Blood 2010;116:Abstact 6. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/6.

40. Kahl BS, Hong F, Williams ME, et al. Results of Eastern Cooperative Oncology Group Protocol E4402 (RESORT): A Randomized Phase III Study Comparing Two Different Rituximab Dosing Strategies for Low Tumor Burden Follicular Lymphoma [abstract]. Blood 2011;118:Abstract LBA-6. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/118/21/LBA-6.

41. Solal-Celigny P, Bellei M, Marcheselli L, et al. Watchful waiting in low-tumor burden follicular lymphoma in the rituximab era: results of an F2-study database. J Clin Oncol 2012;30:3848-3853. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23008294.

42. Colombat P, Salles G, Brousse N, et al. Rituximab (anti-CD20 monoclonal antibody) as single first-line therapy for patients with follicular lymphoma with a low tumor burden: clinical and molecular evaluation. Blood 2001;97:101-106. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11133748.

43. Witzig TE, Vukov AM, Habermann TM, et al. Rituximab therapy for patients with newly diagnosed, advanced-stage, follicular grade I non-Hodgkin's lymphoma: a phase II trial in the North Central Cancer Treatment Group. J Clin Oncol 2005;23:1103-1108. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15657404.

44. McLaughlin P, Grillo-Lopez AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol 1998;16:2825-2833. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9704735.

45. Czuczman MS, Grillo-Lopez AJ, White CA, et al. Treatment of patients with low-grade B-cell lymphoma with the combination of chimeric anti-CD20 monoclonal antibody and CHOP chemotherapy. J Clin Oncol 1999;17:268-276. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10458242.

46. Czuczman MS, Weaver R, Alkuzweny B, et al. Prolonged clinical and molecular remission in patients with low-grade or follicular non-Hodgkin's lymphoma treated with rituximab plus CHOP chemotherapy: 9-year follow-up. J Clin Oncol 2004;22:4711-4716. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15483015.

47. Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2005;106:3725-3732. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16123223.

48. Marcus R, Imrie K, Belch A, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood 2005;105:1417-1423. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15494430.

49. Marcus R, Imrie K, Solal-Celigny P, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J Clin Oncol 2008;26:4579-4586. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18662969.

50. Schulz H, Bohlius JF, Trelle S, et al. Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis. J Natl Cancer Inst 2007;99:706-714. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17470738.

51. Buske C, Kneba M, Lengfelder E, et al. Front - line combined immuno-chemotherapy (R-CHOP) significantly improves the time to treatment failure and overall survival in elderly patients with advanced stage follicular lymphoma - results of a prospective randomized trial of the german low grade lymphoma study group (GLSG) [abstract] Blood 2006;108:Abstract 482. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/108/11/482.

52. Czuczman MS, Koryzna A, Mohr A, et al. Rituximab in combination with fludarabine chemotherapy in low-grade or follicular lymphoma. J Clin Oncol 2005;23:694-704. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15681517.

53. Forstpointner R, Dreyling M, Repp R, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2004;104:3064-3071. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15284112.

54. McLaughlin P, Hagemeister FB, Rodriguez MA, et al. Safety of fludarabine, mitoxantrone, and dexamethasone combined with rituximab in the treatment of stage IV indolent lymphoma. Semin Oncol

2000;27:37-41. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/11225999.

55. Zinzani PL, Pulsoni A, Perrotti A, et al. Fludarabine plus mitoxantrone with and without rituximab versus CHOP with and without rituximab as front-line treatment for patients with follicular lymphoma. J Clin Oncol 2004;22:2654-2661. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/15159414.

56. Liu Q, Fayad L, Cabanillas F, et al. Improvement of overall and failure-free survival in stage IV follicular lymphoma: 25 years of treatment experience at The University of Texas M.D. Anderson Cancer Center. J Clin Oncol 2006;24:1582-1589. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/16575009.

57. Morschhauser F, Mounier N, Sebban C, et al. Efficacy and safety of the combination of rituximab, fludarabine, and mitoxantrone for rituximab-naive, recurrent/refractory follicular non-Hodgkin lymphoma with high tumor burden: a multicenter phase 2 trial by the Groupe d'Etude des Lymphomes de l'Adulte (GELA) and Groupe Ouest Est des Leucemies et Autres Maladies du Sang (GOELAMS). Cancer 2010;116:4299-4308. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/20549824.

58. Nastoupil L, Sinha R, Byrtek M, et al. A Comparison of the Effectiveness of First-Line Chemoimmunotherapy Regimens for Follicular Lymphoma (FL) Used in the United States [abstract]. Blood 2011;118:Abstract 97. Available at:
http://abstracts.hematologylibrary.org/cgi/content/abstract/118/21/97.

59. Federico M, Luminari S, Dondi A, et al. R-CVP Versus R-CHOP Versus R-FM for the Initial Treatment of Patients With Advanced-Stage Follicular Lymphoma: Results of the FOLL05 Trial Conducted by the Fondazione Italiana Linfomi. J Clin Oncol 2013;31:1506-1513. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23530110.

60. Kalaycio M, Rybicki L, Pohlman B, et al. Risk factors before autologous stem-cell transplantation for lymphoma predict for

secondary myelodysplasia and acute myelogenous leukemia. J Clin Oncol 2006;24:3604-3610. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/16877727.

61. Ketterer N, Salles G, Moullet I, et al. Factors associated with successful mobilization of peripheral blood progenitor cells in 200 patients with lymphoid malignancies. Br J Haematol 1998;103:235-242. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9792315.

62. Micallef IN, Apostolidis J, Rohatiner AZ, et al. Factors which predict unsuccessful mobilisation of peripheral blood progenitor cells following G-CSF alone in patients with non-Hodgkin's lymphoma. Hematol J 2000;1:367-373. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/11920216.

63. Fowler N, Kahl BS, Lee P, et al. Bortezomib, Bendamustine, and Rituximab in Patients With Relapsed or Refractory Follicular Lymphoma: The Phase II VERTICAL Study. J Clin Oncol 2011;29:3389-3395. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21810687.

64. Friedberg JW, Vose JM, Kelly JL, et al. The combination of bendamustine, bortezomib, and rituximab for patients with relapsed/refractory indolent and mantle cell non-Hodgkin lymphoma. Blood 2011;117:2807-2812. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/21239695.

65. Friedberg JW, Cohen P, Chen L, et al. Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin's lymphoma: results from a phase II multicenter, single-agent study. J Clin Oncol 2008;26:204-210. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/18182663.

66. Kahl BS, Bartlett NL, Leonard JP, et al. Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma: results from a multicenter study. Cancer 2010;116:106-114. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19890959.

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67. Robinson KS, Williams ME, van der Jagt RH, et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma. J Clin Oncol 2008;26:4473-4479. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18626004.

68. Rummel MJ, Kaiser U, Balser C, et al. Bendamustine plus rituximab versus fludarabine plus rituximab in patients with relapsed follicular, indolent and mantle cell lymphomas - final results of the randomized phase III study NHL 2-2003 on behalf of the StiL (Study Group Indolent Lymphomas, Germany) [abstract]. Blood 2010;116:Abstract 856. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/856.

69. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet 2013;381:1203-1210. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23433739.

70. Flinn IW, Van der Jagt RH, Kahl BS, et al. An Open-Label, Randomized Study of Bendamustine and Rituximab (BR) Compared with Rituximab, Cyclophosphamide, Vincristine, and Prednisone (R-CVP) or Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) in First-Line Treatment of Patients with Advanced Indolent Non-Hodgkin's Lymphoma (NHL) or Mantle Cell Lymphoma (MCL): The Bright Study [abstract]. Blood 2012;120:Abstract 902. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/120/21/902.

71. Witzig TE, Wiernik PH, Moore T, et al. Lenalidomide oral monotherapy produces durable responses in relapsed or refractory indolent non-Hodgkin's Lymphoma. J Clin Oncol 2009;27:5404-5409. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19805688.

72. Leonard J, Jung S-H, Johnson JL, et al. CALGB 50401: A randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma [abstract]. J Clin

Oncol 2012;30:Abstract 8000. Available at: http://meeting.ascopubs.org/cgi/content/abstract/30/15_suppl/8000.

73. Fowler NH, Neelapu SS, Hagemeister FB, et al. Lenalidomide and Rituximab for Untreated Indolent Lymphoma: Final Results of a Phase II Study [abstract]. Blood 2012;120:Abstract 901. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/120/21/901.

74. Witzig TE, Flinn IW, Gordon LI, et al. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. J Clin Oncol 2002;20:3262-3269. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12149300.

75. Witzig TE, Gordon LI, Cabanillas F, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol 2002;20:2453-2463. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12011122.

76. Gordon LI, Witzig T, Molina A, et al. Yttrium 90-labeled ibritumomab tiuxetan radioimmunotherapy produces high response rates and durable remissions in patients with previously treated B-cell lymphoma. Clin Lymphoma 2004;5:98-101. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15453924.

77. Scholz CW, Pinto A, Linkesch W, et al. 90Yttrium ibritumomab tiuxetan as first line treatment for follicular lymphoma. first results from an international phase II clinical trial [abstract]. Blood 2010;116:Abstract 593. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/593.

78. Scholz CW, Pinto A, Linkesch W, et al. (90)Yttrium-ibritumomab-tiuxetan as first-line treatment for follicular lymphoma: 30 months of follow-up data from an international multicenter phase II clinical trial. J Clin Oncol 2013;31:308-313. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23233718.

79. Kaminski MS, Tuck M, Estes J, et al. 131I-tositumomab therapy as initial treatment for follicular lymphoma. N Engl J Med 2005;352:441-449. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15689582.

80. Vose JM, Wahl RL, Saleh M, et al. Multicenter phase II study of iodine-131 tositumomab for chemotherapy-relapsed/refractory low-grade and transformed low-grade B-cell non-Hodgkin's lymphomas. J Clin Oncol 2000;18:1316-1323. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10715303.

81. Kaminski MS, Zelenetz AD, Press OW, et al. Pivotal study of iodine I 131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. J Clin Oncol 2001;19:3918-3328. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11579112.

82. Horning SJ, Younes A, Jain V, et al. Efficacy and safety of tositumomab and iodine-131 tositumomab (Bexxar) in B-cell lymphoma, progressive after rituximab. J Clin Oncol 2005;23:712-719. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15613695.

83. Kaminski MS, Tuck M, Estes J, et al. Tositumomab and iodine I-131 tositumomab for previously untreated, advanced-stage, follicular lymphoma: median 10 year follow-up results [abstract]. Blood 2009;114:Abstract 3759. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/114/22/3759.

84. Kaminski MS, Zelenetz AD, Press OW, et al. Tositumomab and I 131 Tositumomab achieves complete remissions lasting > 10 years in patients with chemotherapy-refractory low-grade and transformed B-cell lymphomas [abstract]. Blood 2010;116:Abstract 3960. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/3960.

85. Pauls SD, Lafarge ST, Landego I, et al. The phosphoinositide 3-kinase signaling pathway in normal and malignant B cells: activation mechanisms, regulation and impact on cellular functions. Front Immunol 2012;3:224. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22908014.

86. Lannutti BJ, Meadows SA, Herman SE, et al. CAL-101, a p110delta selective phosphatidylinositol-3-kinase inhibitor for the treatment of B-cell malignancies, inhibits PI3K signaling and cellular viability. Blood 2011;117:591-594. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20959606.

87. Gopal AK, Kahl BS, de Vos S, et al. PI3Kdelta inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med 2014;370:1008-1018. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24450858.

88. Full prescribing information for idelalisib. 2014 Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206545lbl.pdf.

89. Hainsworth JD, Spigel DR, Markus TM, et al. Rituximab plus short-duration chemotherapy followed by Yttrium-90 Ibritumomab tiuxetan as first-line treatment for patients with follicular non-Hodgkin lymphoma: a phase II trial of the Sarah Cannon Oncology Research Consortium. Clin Lymphoma Myeloma 2009;9:223-228. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19525191.

90. Jacobs SA, Swerdlow SH, Kant J, et al. Phase II trial of short-course CHOP-R followed by 90Y-ibritumomab tiuxetan and extended rituximab in previously untreated follicular lymphoma. Clin Cancer Res 2008;14:7088-7094. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18981007.

91. Morschhauser F, Radford J, Van Hoof A, et al. Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma. J Clin Oncol 2008;26:5156-5164. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18854568.

92. Zinzani PL, Tani M, Pulsoni A, et al. Fludarabine and mitoxantrone followed by yttrium-90 ibritumomab tiuxetan in previously untreated patients with follicular non-Hodgkin lymphoma trial: a phase II non-

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randomised trial (FLUMIZ). Lancet Oncol 2008;9:352-358. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18342572.

93. Leonard JP, Coleman M, Kostakoglu L, et al. Abbreviated chemotherapy with fludarabine followed by tositumomab and iodine I 131 tositumomab for untreated follicular lymphoma. J Clin Oncol 2005;23:5696-5704. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16110029.

94. Press OW, Unger JM, Braziel RM, et al. Phase II trial of CHOP chemotherapy followed by tositumomab/iodine I-131 tositumomab for previously untreated follicular non-Hodgkin's lymphoma: five-year follow-up of Southwest Oncology Group Protocol S9911. J Clin Oncol 2006;24:4143-4149. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16896003.

95. Press OW, Unger JM, Braziel RM, et al. A phase 2 trial of CHOP chemotherapy followed by tositumomab/iodine I 131 tositumomab for previously untreated follicular non-Hodgkin lymphoma: Southwest Oncology Group Protocol S9911. Blood 2003;102:1606-1612. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12738671.

96. Link BK, Martin P, Kaminski MS, et al. Cyclophosphamide, vincristine, and prednisone followed by tositumomab and iodine-131-tositumomab in patients with untreated low-grade follicular lymphoma: eight-year follow-up of a multicenter phase II study. J Clin Oncol 2010;28:3035-3041. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20458031.

97. Morschhauser F, Radford J, Van Hoof A, et al. 90Yttrium-Ibritumomab Tiuxetan Consolidation of First Remission in Advanced-Stage Follicular Non-Hodgkin Lymphoma: Updated Results After a Median Follow-Up of 7.3 Years From the International, Randomized, Phase III First-Line Indolent Trial. J Clin Oncol 2013;31:1977-1983. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23547079.

98. Ghielmini M, Schmitz SH, Cogliatti SB, et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases

event-free survival and response duration compared with the standard weekly x 4 schedule. Blood 2004;103:4416-4423. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14976046.

99. Martinelli G, Hsu Schmitz SF, Utiger U, et al. Long-term follow-up of patients with follicular lymphoma receiving single-agent rituximab at two different schedules in trial SAKK 35/98. J Clin Oncol 2010;28:4480-4484. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20697092.

100. Taverna CJ, Bassi S, Hitz F, et al. Rituximab maintenance treatment for a maximum of 5 years in follicular lymphoma: safety analysis of the randomized phase III trial SAKK 35/03. Blood 2010;116:1802. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/1802.

101. Hainsworth JD, Litchy S, Shaffer DW, et al. Maximizing therapeutic benefit of rituximab: maintenance therapy versus re-treatment at progression in patients with indolent non-Hodgkin's lymphoma--a randomized phase II trial of the Minnie Pearl Cancer Research Network. J Clin Oncol 2005;23:1088-1095. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15657401.

102. Hochster H, Weller E, Gascoyne RD, et al. Maintenance rituximab after cyclophosphamide, vincristine, and prednisone prolongs progression-free survival in advanced indolent lymphoma: results of the randomized phase III ECOG1496 Study. J Clin Oncol 2009;27:1607-1614. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19255334.

103. Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. Lancet 2011;377:42-51. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21176949.

104. Forstpointner R, Unterhalt M, Dreyling M, et al. Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients

with recurring and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG). Blood 2006;108:4003-4008. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16946304.

105. van Oers MHJ, Klasa R, Marcus RE, et al. Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: results of a prospective randomized phase 3 intergroup trial. Blood 2006;108:3295-3301. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16873669.

106. van Oers MHJ, Van Glabbeke M, Giurgea L, et al. Rituximab maintenance treatment of relapsed/resistant follicular non-Hodgkin's lymphoma: long-term outcome of the EORTC 20981 phase III randomized intergroup study. J Clin Oncol 2010;28:2853-2858. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20439641.

107. Freedman AS, Neuberg D, Mauch P, et al. Long-term follow-up of autologous bone marrow transplantation in patients with relapsed follicular lymphoma. Blood 1999;94:3325-3333. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10552941.

108. Rohatiner AZS, Nadler L, Davies AJ, et al. Myeloablative therapy with autologous bone marrow transplantation for follicular lymphoma at the time of second or subsequent remission: long-term follow-up. J Clin Oncol 2007;25:2554-2559. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17515573.

109. Schouten HC, Qian W, Kvaloy S, et al. High-dose therapy improves progression-free survival and survival in relapsed follicular non-Hodgkin's lymphoma: results from the randomized European CUP trial. J Clin Oncol 2003;21:3918-3927. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14517188.

110. Sebban C, Brice P, Delarue R, et al. Impact of rituximab and/or high-dose therapy with autotransplant at time of relapse in patients with

follicular lymphoma: a GELA study. J Clin Oncol 2008;26:3614-3620. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18559872.

111. Peniket AJ, Ruiz de Elvira MC, Taghipour G, et al. An EBMT registry matched study of allogeneic stem cell transplants for lymphoma: allogeneic transplantation is associated with a lower relapse rate but a higher procedure-related mortality rate than autologous transplantation. Bone Marrow Transplant 2003;31:667-678. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12692607.

112. van Besien K, Loberiza FR, Bajorunaite R, et al. Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. Blood 2003;102:3521-3529. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12893748.

113. Hari P, Carreras J, Zhang M-J, et al. Allogeneic transplants in follicular lymphoma: higher risk of disease progression after reduced-intensity compared to myeloablative conditioning. Biol Blood Marrow Transplant 2008;14:236-245. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18215784.

114. Bishu S, Quigley JM, Bishu SR, et al. Predictive value and diagnostic accuracy of F-18-fluoro-deoxy-glucose positron emission tomography treated grade 1 and 2 follicular lymphoma. Leuk Lymphoma 2007;48:1548-1555. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17701586.

115. Blum RH, Seymour JF, Wirth A, et al. Frequent impact of [18F]fluorodeoxyglucose positron emission tomography on the staging and management of patients with indolent non-Hodgkin's lymphoma. Clin Lymphoma 2003;4:43-49. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12837154.

116. Karam M, Novak L, Cyriac J, et al. Role of fluorine-18 fluoro-deoxyglucose positron emission tomography scan in the evaluation and follow-up of patients with low-grade lymphomas. Cancer 2006;107:175-183. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16721817.

117. Wohrer S, Jaeger U, Kletter K, et al. 18F-fluoro-deoxy-glucose positron emission tomography (18F-FDG-PET) visualizes follicular lymphoma irrespective of grading. Ann Oncol 2006;17:780-784. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16497824.

118. Janikova A, Bolcak K, Pavlik T, et al. Value of [18F]fluorodeoxyglucose positron emission tomography in the management of follicular lymphoma: the end of a dilemma? Clin Lymphoma Myeloma 2008;8:287-293. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18854283.

119. Zinzani PL, Musuraca G, Alinari L, et al. Predictive role of positron emission tomography in the outcome of patients with follicular lymphoma. Clin Lymphoma Myeloma 2007;7:291-295. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17324337.

120. Le Dortz L, De Guibert S, Bayat S, et al. Diagnostic and prognostic impact of 18F-FDG PET/CT in follicular lymphoma. Eur J Nucl Med Mol Imaging 2010;37:2307-2314. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20717826.

121. Trotman J, Fournier M, Lamy T, et al. Positron emission tomography-computed tomography (PET-CT) after induction therapy is highly predictive of patient outcome in follicular lymphoma: analysis of PET-CT in a subset of PRIMA trial participants. J Clin Oncol 2011;29:3194-3200. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21747087.

122. Dupuis J, Berriolo-Riedinger A, Julian A, et al. Impact of [18F]Fluorodeoxyglucose Positron Emission Tomography Response Evaluation in Patients With High-Tumor Burden Follicular Lymphoma Treated With Immunochemotherapy: A Prospective Study From the Groupe d'Etudes des Lymphomes de l'Adulte and GOELAMS. J Clin Oncol 2012;30:4317-4322. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23109699.

123. Noy A, Schoder H, Gonen M, et al. The majority of transformed lymphomas have high standardized uptake values (SUVs) on positron emission tomography (PET) scanning similar to diffuse large B-cell lymphoma (DLBCL). Ann Oncol 2009;20:508-512. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19139176.

124. Oh YK, Ha CS, Samuels BI, et al. Stages I-III follicular lymphoma: role of CT of the abdomen and pelvis in follow-up studies. Radiology 1999;210:483-486. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10207433.

125. Zinzani PL, Stefoni V, Tani M, et al. Role of [18F]fluorodeoxyglucose positron emission tomography scan in the follow-up of lymphoma. J Clin Oncol 2009;27:1781-1787. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19273712.

126. Peterson BA, Petroni GR, Frizzera G, et al. Prolonged single-agent versus combination chemotherapy in indolent follicular lymphomas: a study of the cancer and leukemia group B. J Clin Oncol 2003;21:5-15. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12506163.

127. Al-Tourah AJ, Gill KK, Chhanabhai M, et al. Population-based analysis of incidence and outcome of transformed non-Hodgkin's lymphoma. J Clin Oncol 2008;26:5165-5169. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18838711.

128. Yuen AR, Kamel OW, Halpern J, Horning SJ. Long-term survival after histologic transformation of low-grade follicular lymphoma. J Clin Oncol 1995;13:1726-1733. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7602362.

129. Villa D, Crump M, Panzarella T, et al. Autologous and allogeneic stem-cell transplantation for transformed follicular lymphoma: a report of the Canadian blood and marrow transplant group. J Clin Oncol 2013;31:1164-1171. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23401459.

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Marginal Zone Lymphomas

Marginal zone lymphomas (MZLs) are a group of B-cell malignancies thought to originate from B lymphocytes that are normally present in the marginal zone of lymphoid follicles that can be found in the spleen, lymph nodes, and mucosal lymphoid tissues.[1,2] Three distinct subtypes of MZLs exist, which include extranodal MZL of mucosa-associated lymphoid tissue (MALT lymphoma), nodal MZL, and splenic MZL.[3-5] MZLs comprise about 10% of all non-Hodgkin's lymphomas (NHLs), with MALT lymphomas being the most common subtype (occurring in 7-8% of NHLs); nodal MZLs occur in <2% and splenic MZLs in <1% of NHLs.[6] Recent analysis from the SEER database suggested that survival outcomes were more favorable for patients with MALT lymphoma (5-year relative survival 89%) compared with those with splenic MZL (80%) or nodal MZL (76.5%).[7]

The etiology of MZLs has been associated with chronic immune stimulation due to infectious pathogens or inflammation; infection with *Helicobacter pylori (H. Pylori)* has been implicated in cases of gastric MALT lymphoma, and other pathogens such as *Chlamydia psittaci, Campylobacter jejuni, Borrelia burgdorferi*, and hepatitis C virus (HCV) have also been implicated in the putative pathogenesis of MZLs.[1,4] Positive HCV serology has been associated with MZLs (primarily splenic MZL) in about 30% of cases.[8,9] In addition, HCV positivity has also been reported in about 35% of patients with non-gastric MALT lymphomas.[10]

Since MZL are also characterized by clinical and pathological features that overlap with Waldenström's Macroglobulinemia/lymphoplasmacytic lymphoma (WM/LPL), it can be difficult to distinguish WM/LPL from MZLs in selected circumstances.[11] Recent studies have confirmed that the MYD88 L265P somatic mutation which is widely prevalent in patients with WM/LPL could be useful in differentiating WM/LPL from other B-cell malignancies with overlapping clinical and pathological features.[12-14] In a retrospective study that analyzed the immunoglobulin heavy chain variable (*IGHV*) gene sequences and MYD88 mutation status in a series of 123 patients with a diagnosis of MZLs and WM/LPL, MYD88 mutation was found in 67% of patients with WM/LPL (18 of 27) compared to 4% of patients with splenic MZLs (2 out of 53), 7% of patients with MALT lymphomas (2 out of 28) and 0% of patients with nodal MZLs.[13] *IGHV* analysis clearly distinguished splenic MZLs and WM/LPL. Splenic MZLs were characterized by overrepresentation of *IGHV1-2* gene rearrangements with low or intermediate mutation rates whereas WM/LPL was associated with overrepresentation of *IGHV3-23* rearrangements and high mutation rates.[13] In selected circumstances when plasmacytic differentiation is present, MYD88 mutational analysis should be considered to differentiate MZLs from WM/LPL.

The following sections provide a brief summary of the diagnosis, workup, and treatment recommendations for the three subtypes of MZL: MALT lymphomas (gastric and non-gastric), nodal MZL, and splenic MZL.

MALT Lymphomas

In MALT lymphomas, the gastrointestinal (GI) tract is the most common site of involvement (about 50% of MALT lymphomas) and within the GI tract, the stomach is the most common primary site (80-80% of gastric MALT lymphomas).[4,15,16] Common non-gastric sites of involvement in MALT lymphomas include the orbit (7-12%), lung (8-14%), and skin (9-12%).[15-17] MALT lymphomas tend to be indolent, with similar long-term outcomes reported between gastric and non-gastric subtypes. In a retrospective analysis of data from patients with MALT lymphomas

(N=108), the 10-year overall survival (OS) was not different between patients with gastric MALT lymphoma and non-gastric lymphoma (75% vs. 77%).[16] However, in this analysis, gastric MALT lymphoma was associated with longer time to progression (TTP) from start of treatment than non-gastric presentations (median TTP 8.9 years vs. 4.9 years; P=0.01).[16] In a more recent retrospective study in patients with MALT lymphomas (N=98), gastric MALT lymphoma was associated with higher 3-year progression-free survival (PFS) compared with non-gastric cases (95% vs. 82%).[18] In another retrospective study of patients with non-gastric MALT lymphomas (N=180), the 5-year progression-free survival (PFS) and OS was 60% and 90%, respectively.[17] Although disease is localized in most patients with MALT lymphomas, about a third of patients present with disseminated disease; localized disease is more frequently observed with gastric MALT lymphomas than with non-gastric cases.[17,19] Bone marrow involvement has been reported in about 15 to 20% of MALT lymphomas.[15,17,19] In a retrospective analysis of patients with MALT lymphomas (N=158), similar long-term survival was observed between patients with disseminated and localized disease (10-year OS rate 80% in both cases).[19] Recent retrospective data, however, reported decreased PFS outcomes in patients with advanced MALT lymphomas compared with localized disease (3-year PFS rate 73% vs. 94%).[18]

A variety of chromosomal translocations have been implicated in the pathogenesis of MALT lymphomas.[20] t(11;18) is the most common translocation resulting in the formation of the chimeric fusion gene, API2-MALT1 and is frequently detected in gastric and pulmonary MALT lymphomas.[21,22] t(1;14) results in the overexpression of BCL10 protein and it occurs in 1% to 2% of MALT lymphomas.[23] This translocation has been detected in MALT lymphomas of the stomach, lung and skin. Both t(11;18) and BCL10 overexpression are associated with locally

advanced disease, which is less likely to respond to H. Pylori eradication with antibiotic therapy.[24] t(14;18) results in the deregulated expression of MALT1 gene and has been reported to occur in 15% to 20% of MALT lymphomas.[22,25] It is most frequently detected in MALT lymphomas of the liver, skin, ocular adnexa and the salivary gland. t(3;14) results in the upregulation of FOXP1 gene and is associated with the MALT lymphomas of thyroid, ocular adnexa and skin.[26] The clinical significance of t(14;18) and t (3;14) is unknown.

Gastric MALT Lymphoma

Diagnosis
Common clinical features of gastric MALT lymphoma include symptoms of dyspepsia, reflux, abdominal pain, nausea, or weight loss.[1] An endoscopic biopsy is required to establish the diagnosis of gastric MALT lymphoma, as a fine-needle aspiration is not adequate for diagnosis. Endoscopy may reveal erythema, erosions or ulcerations.[1] Adequate hematopathology review of biopsy material and immunophenotyping are needed to establish a diagnosis. The recommended markers for an immunohistochemistry (IHC) panel includes CD20, CD3, CD5, CD10, CD21 or CD23, kappa/lambda, CCND1, BCL2, and BCL6; the recommended markers for flow cytometry analysis include CD19, CD20, CD5, CD23, and CD10. The typical immunophenotype for MALT lymphoma is CD5-, CD10-, CD20+, CD23-/+, CD43 -/+, cyclin D1-, and BCL2 follicles-.

H. pylori infection has a critical role in the pathogenesis of gastric MALT lymphomas and its eradication can lead to tumor remission.[1,27,28] Therefore, staining for detection of *H. pylori* should be performed. However, *H. Pylori* infection is not evident in approximately 5-10% of patients with gastric MALT lymphomas and the translocation t(11;18) was reported to occur at a high frequency in *H. pylori*-negative patients

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with gastric MALT lymphomas.[29] This chromosomal abnormality has been associated with disseminated disease and resistance to antibiotic treatment in patients with gastric MALT lymphoma.[30,31] Molecular analysis by PCR or FISH for the evaluation of t(11;18) is recommended. In some cases, molecular analysis for the detection of antigen receptor gene rearrangements and cytogenetic or FISH evaluation for t(3;14), t(1;14) and t(14;18), may also be useful.

Workup
The initial workup for patients with gastric MALT lymphoma is similar to the workup for other NHLs. A comprehensive physical examination should be performed with attention to non-gastric sites such as the eyes and skin, and performance status should be assessed. Laboratory evaluations should include a complete blood count with differentials and platelets, comprehensive metabolic panel, and measurement of serum LDH levels. Evaluation of bone marrow biopsy, with or without aspirates, may be useful under certain circumstances. Special aspects of the workup for gastric MALT lymphoma include direct endoscopic assessment of the GI tract and additional evaluation of the tumor specimen for the presence of *H.pylori.* If the *H.pylori* infection status is negative based on histopathology evaluation, other non-invasive testing methods may be employed to confirm negative status (i.e., stool antigen test, urea breath test, or blood antibody test) or to establish non-invasive surrogates for upper GI endoscopy. Non-diagnostic atypical lymphoid infiltrates that are *H.pylori* positive should be re-biopsied to confirm or exclude lymphoma prior to treatment of *H.pylori*. Testing for HBV is indicated for patients being considered for treatment with rituximab-containing regimens due to the risk of viral reactivation. Testing for HCV may be useful in selected cases, and given its association with other MZLs and demonstrated importance as a therapeutic target, HCV testing should be performed.

Appropriate imaging studies include CT scan with contrast of diagnostic quality for the chest, abdomen and pelvis. At some NCCN institutions, endoscopic ultrasound (EUS) is used to complement conventional endoscopy at the time of the initial workup and at follow-up. EUS also provides information regarding the depth of involvement in the gastric wall which provides essential information for some of the currently used staging systems; it also helps to distinguish benign lymphoid aggregates from lymphoma associated with *H. pylori* infection.[32] In addition, EUS staging is also useful in predicting the efficacy of *H. Pylori* eradication therapy.[33,34] EUS with multiple biopsies of anatomic sites is particularly useful for H. pylori-positive patients because the likelihood of tumor response to antibiotic therapy is related to depth of tumor invasion. A MUGA scan/echocardiogram should be performed if the patient is being considered for treatment with regimens containing anthracycline or anthracenedione.

Staging can remain a challenge, as it is not standardized for MALT lymphomas; because CT scans may not be optimal for the detection of occult extranodal disease, it is unknown whether staging for MALT lymphomas should follow standard staging systems (e.g., Ann Arbor system) used for nodal-type lymphomas.[1,2] Several different staging systems have been used for gastric MALT lymphomas. The widely used Lugano Staging System for GI lymphomas is a modification of the original Ann Arbor stating system.[35] In the Lugano Staging, stage I refers to disease confined to the GI tract (single primary or multiple non-contiguous lesions; in Stage I_1, the infiltration is limited to mucosa with or without submucosa involvement, and in Stage I_2, infiltration is present in the muscularis propria, serosa or both. Stage II refers to disease extending into the abdomen from the primary GI site; in Stage II_1, local (perigastric) lymph nodes are involved, and in Stage II_2, distant lymph nodes are involved. Stage IIE refers to lymphoma penetration of

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serosa to involve adjacent organs or tissues; if both the lymph nodes and adjacent organs are involved, the above subscripts (1 or 2) for lymph node involvement may be added to the designation. Ann Arbor stage III has been removed, and stage IV in the Lugano Staging refers to disseminated extranodal involvement or concomitant supradiaphragmatic nodal involvement. The TNM staging system corresponds to the staging in gastric cancer and the depth of the lymphoma infiltration is measured by EUS. Involvement of multiple extranodal sites in MALT lymphoma appears to be biologically distinct from multiple extranodal involvements in other lymphomas, and these patients may be managed by treating each site separately with excision or RT or with rituximab. By contrast, cases with disseminated nodal involvement appear to behave more like nodal MZL or like disseminated follicular lymphoma (FL).

Treatment Options Based on Clinical Stage
The treatment approach for gastric MALT lymphomas depends on the *H. pylori* infection status and disease stage. *H.pylori* infection plays a central role in the pathogenesis of some cases of gastric MALT lymphoma. The efficacy of antibiotic therapy for the treatment for gastric MALT lymphoma has been evaluated in a number of retrospective and prospective studies.[36-43] In these studies, *H.pylori* eradication with antibiotic therapy resulted in lymphoma regression in 70-95% of patients with localized disease. In studies with long-term follow up, the 5-year OS rate with *H.pylori* eradication therapy was 90-95%, with a 5-year disease-free survival (DFS) or event-free survival (EFS) rate of 75-80%.[38,40,42] However, there is increasing evidence that late relapses can occur after antibiotic treatment and a long duration of follow-up is appropriate. If there is evidence of t(11;18), t(1;14) or t(14;18), treatment of the *H.pylori* infection with antibiotics may be ineffective; these patients should be considered for alternative therapy, though a

trial of antibiotics is still warranted in some patients.[30] *H.pylori* eradication therapy generally comprises a proton pump inhibitor (e.g., omeprazole or other agents such as lansoprazole or rabeprazole) along with a combination of antibiotics including clarithromycin and amoxicillin (or metronidazole for patients allergic to penicillin).[1]

Radiation therapy (RT) has been evaluated in patients with both gastric and non-gastric MALT lymphomas. In a retrospective study of patients who received treatment for localized MALT lymphomas (N=103; lymphoma of the stomach, n=17), the CR rate was 99% in the group of patients treated with involved field RT (IFRT; dose range 30-35 Gy) only (n=85).[44] The 5-year DFS and OS rates were 77% and 98%, respectively. The median follow up for patients treated with RT alone was 4.9 years. Among the patients with gastric MALT lymphoma or primary involvement of the thyroid, none had relapsed at the time of last follow up (failure-free survival rate 100%).[44] Long-term outcomes from this study with a median follow up of 7 years showed that patients with localized MALT lymphoma who received IFRT alone (n=144; dose range 25-35 Gy) had an estimated 10-year relapse-free rate and OS rate of 74% and 89%, respectively.[45] The estimated 10-year cancer-specific OS rate was 98%. Similar to the previous report,[44] outcomes were more favorable for patients with gastric or thyroid MALT lymphoma (n=46); the 10-year relapse-free rate for these patients was 89% compared with 68% for patients with lymphomas in other sites (*P*=0.004).[45]

In another retrospective study in patients with localized gastric MALT lymphoma (N=115), initial therapy with RT alone (n=56) resulted in a CR rate of 96% and a 10-year cancer-specific OS rate of 94%.[46] Several studies suggested that RT may preclude the need for surgical resection and that surgery does not offer an advantage over other treatment modalities. In the randomized controlled study in patients with

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localized gastric MALT lymphomas (N=241), the 10-year EFS rates for the groups randomized to treatment with surgery (n=80), RT (n=78), and chemotherapy (n=83) were 52%, 52%, and 87%, respectively (*P*<0.01).[47] The median follow up in this study was 7.5 years. The 10-year OS rate was not significantly different between the groups treated with surgery, RT or chemotherapy (80% vs. 75% vs. 87%, respectively).[47] In an analysis of registry data from a German multicenter study in patients with localized gastric lymphomas, outcomes were compared between patients treated with RT alone and those treated with combined surgery and RT.[48] In the subgroup of patients with indolent gastric lymphomas (gastric MALT lymphomas, n=151), extended field RT (total dose 30 Gy followed by 10 Gy boost) alone resulted in an EFS and OS rate of 88% and 93%, respectively, after a median of 42 months of observation. These outcomes were not significantly different from those of patients with gastric MALT lymphomas who received combined modality therapy with surgery and RT (EFS and OS rates 72% and 82.5%, respectively).[48] This study had also included patients with gastric MALT lymphomas who experienced treatment failure with *H. pylori* eradication therapy. In a small study that evaluated RT alone (median total dose 30 Gy; range, 28.5-43.5 Gy) in patients with gastric MALT lymphoma without evidence of *H. pylori* or with persistent disease after *H. pylori* eradication therapy (N=17), the CR rate was 100% and the EFS rate was 100% after a median follow up of 27 months.[49] Long-term follow up data from other studies suggest that RT is an effective treatment modality in gastric MALT lymphoma after failure with *H. pylori* eradication therapy.[42,46] In the subgroup of patients with gastric MALT lymphomas who were unresponsive to *H. pylori* eradication therapy and underwent second-line therapy with RT (n=10) or single-agent chemotherapy with cyclophosphamide (n=12), the CR rate was 80% and 83%, respectively; the estimated 3-year OS (from start of second-line therapy) was 90% and 88%, respectively.[42] In

a retrospective analysis of data from patients who received RT following treatment failure with *H. pylori* eradication therapy (n=35), the CR rate was 89% and the 5-year cause-specific OS rate was 93%.[46]

Immunotherapy with the anti-CD20 monoclonal antibody rituximab has also been evaluated in the clinical setting of failure with *H. pylori* eradication therapy. A prospective study evaluated the activity of standard-dose rituximab in patients with gastric MALT lymphoma (N=27) relapsed/refractory to *H. pylori* eradication therapy or not eligible for eradication therapy (i.e., *H. pylori* negative disease).[50] The majority of patients (81%) had stage I or II$_1$ disease (Lugano Staging System). The ORR with rituximab was 77% with a CR rate of 46%; at a median follow up of 28 months from start of treatment, all patients were alive and 54% of patients were disease free.[50]

Chemotherapy (single agent or combination regimens) has been evaluated in patients with MALT lymphomas. In an early study of single-agent therapy with the alkylating agents chlorambucil or cyclophosphamide (given orally for 12-24 months) in patients with primarily gastric MALT lymphoma (N=24; advanced stage, n=7), CR was achieved in 75% of patients.[51] In a prospective study that evaluated the purine analog cladribine in patients with MALT lymphoma (N=27; gastric lymphoma, n=19), CR was achieved in 84% of patients.[52] Patients with *H. pylori* positive localized gastric disease underwent eradication therapy and were only enrolled if unresponsive to *H. pylori* eradication treatment. All patients with gastric MALT lymphoma treated with cladribine (n=18) achieved a CR whereas only 43% with non-gastric lymphoma achieved a CR. At a median follow up of 80 months, 84% of patients remained alive.[53] DFS at 6.7 years was 68.5% for all patients, and was higher for patients with gastric MALT lymphoma compared with those with extra-gastric lymphoma (78.5% vs. 33%).[53] Combination chemotherapy with mitoxantrone, chlorambucil and

prednisone (MCP) was retrospectively evaluated in patients with primarily advanced MALT lymphoma (N=15; gastric lymphoma, n=5 only).[54] Among the 5 patients with gastric MALT lymphoma (all were stage I or II), the MCP regimen induced a response in all patients, including a CR in 3 patients who had failed prior *H. pylori* eradication therapy, and a CR in 1 patient who received concurrent *H. pylori* eradication therapy. None of the patients have relapsed after a median follow up of 16 months.[54]

Several studies have evaluated chemoimmunotherapy combination regimens that incorporate rituximab in the treatment of MALT lymphomas.

A retrospective study evaluated rituximab combined with cyclophosphamide, doxorubicin (or mitoxantrone), vincristine, and prednisone (R-CHOP/R-CNOP) in patients with relapsed MALT lymphoma (N=26).[55] CR was achieved in 77% of patients. All patients were alive after a median follow up of 19 months, with 22 patients having ongoing remission.[55] A phase II study evaluated the chemoimmunotherapy combination of fludarabine and rituximab in patients with previously untreated MALT lymphoma (N=22; gastric lymphoma, n=12).[56] Among evaluable patients with gastric MALT lymphoma (n=11), the CR rate was 100% and the 2-year PFS rate was 100%. Another phase II study evaluated a different purine analog cladribine in combination with rituximab in patients with MALT lymphoma (N=40; gastric lymphoma, n=21).[57] The ORR was 81% with CR in 58% of patients. After a median follow up of 17 months, 88% of patients were alive. In the subgroup with gastric MALT, the ORR was 86% with a CR in 76% of patients.[57]

In a non-randomized observational study in patients with gastric MALT lymphoma (N=49), chlorambucil combined with rituximab resulted in

improved remission rates at week 25 compared with rituximab alone (93% vs. 81%); interestingly, this apparent benefit with the combined regimen over rituximab alone was observed in the subgroup with t(11;18) (remission rate at week 25: 100% vs.66%) but not among t(11;18)-negative patients (66% vs. 92%).[58]

The international randomized IELSG-19 trial evaluated the combination of chlorambucil with rituximab in comparison to chlorambucil alone in patients with MALT lymphoma not previously treated with systemic anticancer therapy.[59] Eligible patients included those who were not responding to or not suitable for local therapy. Final data analysis was conducted in patients treated with chlorambucil alone (n=113) and chlorambucil combined with rituximab (n=114). The combination regimen resulted in higher CR rates (78% vs. 65%) and improved 5-year EFS (68% vs. 50%; P=0.002), while the ORR (90% vs. 87%), 5-year PFS (71% vs. 62%) and OS rate (89% in both arms) were not significantly different.[59]

A multicenter phase II trial is investigating the combination of bendamustine and rituximab in patients with previously untreated MALT lymphoma (N=60; gastric lymphoma, n=20).[60] After 3 cycles of combination therapy, the ORR was 100% and CR rate was 76%; gastric lymphoma was associated with a higher CR rate compared with non-gastric disease (90% vs. 64%). The CR rate after completion of treatment was 98%, with most patients (85%) requiring only 4 or fewer cycles of therapy to achieve a CR. After a median follow up of 16 months, all patients remain relapse free and 1 patient died due to neurologic causes.[60]

The proteasome inhibitor bortezomib was evaluated in a phase II study in patients with relapsed/refractory MALT lymphoma (N=32; gastric lymphoma, n=14; median 2 prior therapies).[61] Among evaluable patients

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(n=29), the ORR was 48% with a CR rate of 31%. After a median follow up of 24 months, 5 patients died, including 2 deaths due to disease progression.[61]

Although chemotherapy regimens may be active in patients with MALT lymphomas, long-term data from a larger group of patients are needed to evaluate their role in the management of localized disease. The international randomized LY03 trial of chlorambucil versus observation following *H. pylori* eradication in patients with localized gastric MALT lymphoma (N=110) showed no difference between study arms with regards to recurrence/progression rate, PFS, or OS outcomes.[62] Therefore, in the absence of data showing benefits with chemotherapy, localized gastric MALT lymphoma should be treated with *H. pylori* eradication therapy or RT, as appropriate. Chemotherapy regimens may be considered for patients with relapsed/refractory disease following RT or for those with advanced, systemic disease.[63]

NCCN Recommendations for Stage I-II
Antibiotic therapy in combination with a proton pump inhibitor to block gastric acid secretion is recommended for *H. Pylori*-positive. Patients who are *H. Pylori*-positive with t(11;18) could also be treated with antibiotic therapy to eradicate H. Pylori infection. However, since t(11;18) is a predictor for lack of response to antibiotic therapy, these patients should be considered for alternative therapy for lymphoma as described for patients who are *H. pylori*-negative. ISRT is the preferred treatment option for patients with *H. pylori* negative disease (negative status confirmed by both histology and blood antibody test). Rituximab is an option for patients with contraindications to RT.[50]

Patients treated with antibiotic therapy for *H. pylori* eradication should be restaged with endoscopy and biopsy after 3 months following therapy. Patients with stage IE2 or stage IIE disease with involvement

of submucosa or regional lymph nodes are much less likely to respond to antibiotic therapy. In symptomatic patients after antibiotic therapy, restaging can be done earlier than 3 months and RT may be considered earlier. Patients with responsive disease (*H. pylori* negative and lymphoma negative) can be observed. Patients who are *H. pylori* negative with persistent or recurrent lymphoma are treated with RT, if they are symptomatic. Asymptomatic patients can be observed for another 3 months; alternatively, locoregional RT can be considered as early as 3 months after observation but observation can be prolonged for up to 18 months (category 2B). If the patient initially had clinical stage I2 or stage IIE disease, early RT should be considered if the lymphoma does not regress with antibiotic therapy. Patients with persistent *H. pylori* and regressing or stable lymphoma are treated with second-line antibiotics. Lastly, patients who are *H. pylori* positive with progressive or symptomatic lymphoma should be treated with RT and second-line antibiotics.

Patients treated with initial RT should be restaged with endoscopy and biopsy after 3-6 months following RT. Patients with responsive disease (*H. pylori* negative and lymphoma negative) can be observed. Antibiotic treatment can be considered for patients with persistent *H. pylori* and regressing lymphoma. However, patients with persistent lymphoma (regardless of presence of *H. pylori*) following RT should be managed according to recommendations for FL contained in these NCCN Guidelines for NHL.

Following observation or additional therapy with antibiotic therapy or RT (as discussed above), patients are again evaluated with endoscopy and biopsy after 3 months. The biopsy should rule out evidence of large-cell transformation. Any area of DLBCL should be treated according to recommendations for DLBCL in the NCCN Guidelines for NHL. For patients with a CR, clinical follow-up with

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physical examination and laboratory assessment should be performed every 3-6 months for 5 years and then yearly thereafter (or as clinically indicated). The optimal interval for follow-up endoscopy and imaging is not known. At the present time, follow-up endoscopy and imaging at NCCN institutions are performed as clinically indicated based on symptoms. Patients with no response to second-line RT or recurrence following an initial CR should be treated with systemic therapy according to the guidelines for FL. Locoregional RT is indicated for patients with no response to second-line antibiotic therapy.

NCCN Recommendations for Stage III or IV
In patients with advanced stage disease (which is uncommon), treatment is similar to that described for patients with advanced stage FL. As with FL, asymptomatic patients without indications for treatment are monitored without therapy. The decision to treat is guided by end-organ dysfunction or the presence of symptoms (such as GI bleeding, early satiety), bulky disease at presentation, steady progression of disease, or patient preference. For patients with indications for treatment, enrollment in clinical trial is recommended given the incurability of advanced disease with conventional regimens. In the absence of suitable clinical trials, treatment may include chemoimmunotherapy or locoregional RT (30 Gy). Surgical resection is generally limited to specific clinical situations such as life-threatening hemorrhage. Although disease control is excellent with total gastrectomy, the long-term morbidity has precluded routine surgical resection. If there is evidence of recurrence (by endoscopy) following initial induction therapy, patients should be managed according to the FL guidelines.

Non-gastric MALT Lymphomas
MALT lymphomas can arise from a large number of non-gastric sites such as the bowel (small and large), breast, lung, ocular adnexa, ovary, prostate, parotid, salivary glands and other head and neck regions.[17] The most common sites of presentation include the parotid and salivary glands (18-26%), skin (12-26%), conjunctiva/orbit (7-14%), head and neck (11%), lung (8-9%), thyroid (6%) and breast (2-3%).[17,64] Infectious pathogens (e.g., *Chlamydia psittaci, Campylobacter jejuni*) have been associated with MALT lymphomas of non-gastric sites[4] but testing for these pathogens is not required for disease workup or management.

Diagnosis
Adequate hematopathology review of biopsy materials and immunophenotyping are needed to establish a diagnosis. The recommended markers for an IHC panel include CD20, CD3, CD5, CD10, CD21 or CD23, kappa/lambda, CCND1, and BCL2; the recommended markers for flow cytometry analysis include CD19, CD20, CD5, CD23, and CD10. The typical immunophenotype for MALT lymphoma is CD5-, CD10-, CD20+, CD23-/+, CD43 -/+, cyclin D1-, BCL2-. Molecular analysis to detect antigen receptor gene rearrangement or t(11;18) may be useful in certain cases. In addition, cytogenetics or FISH for t(11;18) t(3;14), t(11;14) and t(14;18) may also be considered under certain circumstances.

Workup
The workup for non-gastric MALT lymphoma is similar to the workup for other NHLs. A comprehensive physical examination should be performed and performance status should be assessed. Laboratory evaluations should include a complete blood count with differentials and platelets, comprehensive metabolic panel, and measurement of serum LDH levels. Evaluation of bone marrow biopsy, with or without aspirates, may be useful for patients with multifocal disease. In addition, endoscopy with multiple biopsies of anatomical sites may be useful in selected cases. Appropriate imaging studies include CT scan (with contrast of diagnostic quality) of the chest, abdomen and pelvis. A

MUGA scan/echocardiogram should be performed if the patient is being considered for treatment with regimens containing anthracycline or anthracenedione. Testing for hepatitis B virus is indicated for patients being considered for treatment with rituximab-containing regimens due to the risk of viral reactivation with chemoimmunotherapy. Testing for HCV may be useful in selected cases.

Treatment Options
As discussed above in the section for 'Gastric MALT Lymphomas', RT alone has been shown to be an effective treatment strategy for both localized gastric and non-gastric MALT lymphomas. In the long-term follow up from a retrospective study in patients with localized MALT lymphomas treated with RT with or without chemotherapy (N=167; non-gastric lymphomas, n=142), the group who received IFRT alone (n=144; dose range 25-35 Gy; 25 Gy for orbit) had an estimated 10-year relapse-free rate and OS rate of 74% and 89%, respectively.[45] The 10-year relapse-free rates for patients with primary involvement of the thyroid (n=21), salivary gland (n=28), and orbital adnexa (n=71) were 95%, 68%, and 67%, respectively.[45]

Other treatment modalities such as chemotherapy (alone or with RT) or surgery (alone or with RT and/or chemotherapy) have been evaluated. In a retrospective study in patients with non-gastric MALT lymphomas (N=180; Ann Arbor stage IV in 27%), patients were treated with chemotherapy (n=78; with or without RT), RT alone (n=41), or surgery (n=68; with or without RT and/or chemotherapy).[17] More than half of patients with early-stage disease were treated with RT (55%; with or without other therapies), including RT alone in 30%; surgery or systemic chemotherapy (with or without other therapies, in both cases) was employed in 42% (surgery alone in 17%) and 31%, respectively. Among patients with advanced disease (stage IV), the large majority were treated with systemic chemotherapy (75.5%; with or without other

therapies); RT alone was used in only 4% of these patients. Surgery (with or without other therapies) was employed in 26.5% of patients with advanced disease, including 10% who received surgery alone.[17] Among evaluable patients (n=174), the ORR to treatment was 93% with a CR rate of 77%. Among patients who received chemotherapy, the ORR and CR rates were 92% and 72%, respectively. After a median follow up of 3.4 years, the estimated 5-year PFS and OS rates were 60% and 90%, respectively. The 5-year PFS and OS rates were both 100% for the subgroup of patients with primary involvement in the conjunctiva (n=18) and thyroid (n=10). In patients with primary disease in the orbit (n=13), however, the corresponding outcomes were 23% and 80%, respectively. For patients with primary disease in the salivary gland (n=46), the 5-year PFS and OS rates were 67% and 97%; for the patients with primary disease in the skin (n=22), the corresponding rates were 53% and 100%, respectively.[17]

In another retrospective study in patients with non-gastric MALT lymphomas (N=208; Ann Arbor stage III-IV in 44%), patients were treated with chemotherapy alone (45%; about half received single-agent alkylating agent while other received combination therapy), surgery (21%), or RT (19%).[64] The ORR to treatment was 90% with a CR rate of 73%. The ORR among patients treated with chemotherapy, RT, or surgery were 65%, 76%, and 90%, respectively. After a median follow up of 2.7 years, the median EFS rate was 2.4 years; the estimated 5-year EFS and OS rates were 37% and 83%, respectively.[64] Among patients with primary disease in the skin (n=55), the 5-year EFS and OS rates were 44% and 100%, respectively. Among patients with primary disease in the salivary glands (n=38), the 5-year EFS and OS rates were 30% and 86%, respectively; for patients with disease in the orbit/conjunctiva (n=30), the corresponding rates were 49% and 100%, respectively. As would be expected, 5-year OS rates were significantly

higher among patients with Ann Arbor stage I-II disease compared with those with stage III-IV disease (94% vs. 69%; P=0.001). On multivariate analysis, bone marrow involvement was the only significant independent predictor of inferior outcomes for both EFS and OS.[64]

Rituximab either alone or in combination with chemotherapy has also been evaluated in patients with previously untreated or relapsed non-gastric MALT lymphoma. The IELSG evaluated the clinical activity of single agent rituximab in a phase II study in patients with untreated as well as relapsed MALT lymphomas (35 patients; 15 patients with gastric MALT lymphoma and 20 patients with non-gastric MALT lymphoma).[65] Among patients with non-gastric MALT lymphoma, treatment with rituximab resulted in an ORR of 80% (55% CR and 25% PR). For the entire study population, the ORR was significantly higher in the chemotherapy-naive patients than in previously treated patients (87% and 45% respectively; P = .03).

A phase II study evaluated the chemoimmunotherapy combination of fludarabine and rituximab in patients with previously untreated MALT lymphoma (N=22).[56] In the primary non-gastric MALT subgroup (n=10), the ORR was 100% with a CR rate of 80%; PFS at 2 years was 89% in this subgroup. Another phase II study evaluated a different purine analog cladribine in combination with rituximab in patients with MALT lymphoma (N=40).[57] In the subgroup with primary non-gastric MALT (n=19), the ORR was 74% with a CR in 37% of patients. The CR rate was lower than that reported for the subgroup with primary gastric MALT (76%).[57]

In the international randomized IELSG-19 trial that compared chlorambucil alone with the combination of chlorambucil and rituximab in patients with MALT lymphoma not previously treated with systemic anticancer therapy, CR rates, EFS, PFS, and OS rates were not significantly different between patients with primary gastric and non-gastric lymphoma in either treatment arm.[59] In the multicenter phase II trial that investigated the combination of bendamustine with rituximab in patients with previously untreated patients with MALT lymphoma (N=60), the CR rate was 64% in the subgroup of patients with primary non-gastric lymphoma (n=35).[60]

NCCN Recommendations
ISRT (24-30 Gy) is the preferred treatment for patients with stage I-II disease. RT dose is site dependent, with lower doses usually reserved for orbital involvement. Rituximab is included as an option for selected patients. RT or observation is appropriate for patients with extranodal involvement. Based on anecdotal responses to antibiotics in ocular and cutaneous MZLs, some physicians may give an empiric course of doxycycline prior to initiating other therapy. Observation may be considered for patients whose diagnostic biopsy was excisional or in whom RT or systemic treatment could result in significant morbidity. For patients with stage I-II disease, surgical excision for adequate diagnosis may be appropriate treatment for certain sites of disease (e.g., lung, thyroid, colon, small intestine, and breast). If there is no residual disease following surgery, patients can be observed; for patients with positive margins post-surgery, locoregional RT should be considered.

Clinical follow-up (including repeat diagnostic tests and imaging based on the site of disease and as clinically indicated) should be conducted every 3-6 months for 5 years and then annually thereafter (or as clinically indicated). Local recurrence following primary treatment may be treated with RT or managed according to recommendations for advanced-stage FL. Systemic recurrence should be managed according to the recommendations for advanced FL, as should patients presenting with stage III-IV disease (extranodal disease and multiple nodal sites) at

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diagnosis. MALT lymphomas coexistent with large-cell lymphoma should be managed according to the recommendations for DLBCL.

Nodal Marginal Zone Lymphoma

In patients with nodal MZL, peripheral lymphadenopathy is present in nearly all cases (>95%); thoracic or abdominal lymph nodes may also be involved in about 50% of cases.[15,66] In addition, involvement of MZL in the bone marrow and peripheral blood may be seen in about 30-40% and 10% of cases, respectively.[15,66] Although advanced-stage disease is observed in about two-thirds of newly diagnosed nodal MZL, most tumors are non-bulky and B symptoms are present in only about 15% of cases.[15,66] The disease course of nodal MZL tends to be indolent, but long-term outcomes appear less favorable compared with MALT lymphomas. In a retrospective analysis of data from patients with MZL, the OS rate was lower in the subgroup of patients with nodal MZL (n=14) compared with those with MALT lymphoma (n=62)(56% vs. 81%); the 5-year failure-free survival rate was also lower among patients with nodal MZL (28% vs. 65%).[15] In a separate retrospective study in patients with non-MALT-type MZL (N=124), the median TTP (from start of treatment) and median OS was 1.3 years and 5.5 years, respectively, among the subgroup of patients with nodal MZL (n=37).[66]

Diagnosis

Adequate hematopathology review of biopsy materials and immunophenotyping are needed to establish a diagnosis. Nodal MZL is rare and occurs most commonly as disseminated disease from extranodal MALT lymphoma. The recommended markers for an IHC panel include CD20, CD3, CD5, CD10, CD21 or CD23, kappa/lambda, CCND1, and BCL2; the recommended markers for flow cytometry include CD19, CD20, CD5, CD23, and CD10. The typical immunophenotype for nodal MZLs is CD5-, CD10-, CD20+, CD23-/+, CD43 -/+, cyclin D1-, BCL2-. Pediatric nodal MZL should be considered

with located disease in young patients. Molecular analysis to detect antigen receptor gene rearrangement or t (11; 18) (by PCR) may be useful in certain cases. In addition, cytogenetics or FISH for t(11;18) t(3;14), t(11;14) , t(14;18), del(13q) and del(7q) may also be considered under certain circumstances.

Workup

The workup for nodal MZLs is similar to the workup for other NHL subtypes. A comprehensive physical examination should be performed and performance status should be assessed. Laboratory evaluations should include a complete blood count with differentials and platelets, comprehensive metabolic panel, and measurement of serum LDH levels. Evaluation of bone marrow biopsy with aspirates should be performed to document clinical stage I-II disease. Bone marrow biopsy may be deferred until treatment is indicated, however. Appropriate imaging studies include CT scan (with contrast of diagnostic quality) of the chest, abdomen and pelvis. Nodal MZL occurs primarily in the lymph nodes, although involvements of additional extranodal sites are common. The diagnosis of nodal MZL requires careful evaluation to rule out extranodal sites of primary disease and must be distinguished from nodal FL, MCL, lymphoplasmacytic lymphoma and CLL, all of which are more common. A MUGA scan/echocardiogram should be performed if the patient is being considered for treatment with regimens containing anthracycline or anthracenedione. Testing for hepatitis B virus is indicated for patients being considered for treatment with rituximab-containing regimens due to the risk of viral reactivation with chemoimmunotherapy. Testing for hepatitis C virus may be useful in select cases.

NCCN Recommendations

The panel recommends that patients with nodal MZL be managed according to the recommendations for FL in the NCCN Guidelines for NHL.

Splenic Marginal Zone Lymphoma

Splenic MZL is characterized by the presence of splenomegaly in all cases, which may become symptomatic when massive or when associated with cytopenias.[2,5,66] Peripheral lymph nodes are generally not involved while splenic hilar lymph nodes are often involved[2,5]; involvement of thoracic or abdominal lymph nodes may also be seen in about a third of patients with splenic MZL.[8,66] In addition, bone marrow involvement is present in the majority of patients (about 85%) and involvement of peripheral blood occurs in 30-50% of patients.[2,8,66] Although most patients with splenic MZL present with advanced-stage disease, the disease course is generally indolent. Among the subgroup of patients with splenic MZL (n=59) in a retrospective study in patients with non-MALT-type MZL, the median TTP (from start of treatment) and median OS was 6.9 years and 9.1 years, respectively.[66] Similarly, in a retrospective review of data from patients with splenic MZL (N=81), the median OS was 10.5 years.[67]

Diagnosis

Adequate hematopathology review of biopsy materials and immunophenotyping are needed to establish a diagnosis. The diagnosis of splenic MZL requires bone marrow involvement with or without peripheral blood involvement by small lymphoid cells with immunoglobulin (Ig) light chain restriction that lack characteristic features of other small B-cell neoplasms (CD5, CD10, cyclin D1).[68] The recommended markers for an IHC panel include CD20, CD3, CD5, CD10, CD21 or CD23, CD43, kappa/lambda, IgD, CCND1, BCL2, and annexin A1; the recommended markers for flow cytometry analysis

include CD19, CD20, CD5, CD23, CD10, CD43, and CD103. The typical immunophenotype for splenic MZL is CD5-, CD10-, CD20+, CD23-/+, CD43-, cyclin D1-, BCL2 follicles-, annexinA1-, CD103-,and with expression of both IgM and IgD. This lymphoma is distinguished from CLL by the absence of CD5 expression, strong CD20 expression and variable CD23 expression, and from hairy cell leukemia (HCL) by the absence of CD103 expression.

Splenic MZL is most definitively diagnosed at splenectomy, since the immunophenotype is nonspecific and morphologic features on the bone marrow may not be diagnostic. However in a patient with splenomegaly (small or no M component) and a characteristic intra sinusoidal lymphocytic infiltration of the bone marrow, the diagnosis can strongly be suggested on bone marrow biopsy, if the immunophenotype is consistent. Plasmacytoid differentiation with cytoplasmic Ig detectable on paraffin sections may occur. In such cases, the differential diagnosis may include LPL. *MYD88* and *BRAF* mutation status can be useful in selected cases for differentiating splenic MZLs from WM/LPL and HCL respectively.[13,69,70] Conventional and real-time allele-specific polymerase chain reaction (AS-PCR) for *MYD88 (L265P)* has been reported to be an useful test to differentiate WM from non-IgM LPL and other B-cell lymphomas with overlapping clinical and pathological features.[71]

Workup

The initial workup for splenic MZL is similar to the other indolent lymphomas. A comprehensive physical examination should be performed and performance status should be assessed. Laboratory evaluations should include a complete blood count with differentials and platelets, comprehensive metabolic panel, and measurement of serum LDH levels. Serum protein electrophoresis (SPEP) and/or measurement of quantitative immunoglobulin levels should be performed. If elevated

immunoglobulins or monoclonal immunoglobulin is detected, further characterization by immunofixation of blood may be useful. Evaluation of bone marrow biopsy with or without aspirates should be performed.

Appropriate imaging studies include CT scan (with contrast of diagnostic quality) of the chest, abdomen and pelvis. A MUGA scan/echocardiogram should be performed if the patient is being considered for treatment with regimens containing anthracycline or anthracenedione. Testing for HCV is an essential part of initial workup. Hepatitis C has been associated with and implicated in the pathogenesis of splenic MZL and should be evaluated for all patients suspected of having this diagnosis.[72] Testing for HBV is indicated for patients being considered for treatment with rituximab-containing regimens due to the risk of viral reactivation. Other useful evaluations may include cryoglobulin testing for detection of abnormal proteins frequently associated with hepatitis C, and direct Coombs test for evaluation of autoimmune hemolytic anemia.

Treatment Options

As previously mentioned, HCV infection may be associated with some cases of MZLs. In a retrospective study in patients with MZLs, positive HCV serology was detected in 35% of the group of patients with splenic MZL.[8] Antiviral therapy with interferon (IFN)-alfa, with or without ribavirin, has been shown to induce virologic and hematologic responses in patients with HCV-positive MZLs, including in those with splenic disease.[8,73-75] A recent retrospective study evaluated the activity of antiviral therapy with IFN or pegylated-IFN, with or without ribavirin (84% received ribavirin), in a large series of patients with HCV-positive indolent B-cell NHLs (N=94; splenic MZL histology, n=30 [32%]).[76] Among the patients who received antiviral treatment as first-line therapy (n=76; splenic MZL, n=24), the ORR and CR rate was 77% and 47%, respectively, and a sustained virologic response was observed in 78%

of patients. The median duration of response was 23 months after a median follow up of 3.3 years. The 5-year PFS and OS rate was 78% and 94%, respectively.[76]

For patients with splenic MZL with negative HCV serology, various treatment modalities including splenectomy, single-agent chemotherapy, combination chemotherapy, immunotherapy with rituximab, and/or chemoimmunotherapy (rituximab combined with chemotherapy) have been evaluated. About 20% to 25% of patients may be observed without initiating treatment at diagnosis, in the absence of disease symptoms or cytopenias.[67,77] Splenectomy alone can result in an ORR of 80% to 90%, with a median OS of 93 months reported in retrospective series.[77,78] Splenectomy with adjuvant chemotherapy (e.g., CHOP-like regimens, alkylating agents, purine analogs) resulted in CR rates of about 50%, with median OS of 107.5 months (about 9 years).[78,79] In retrospective studies, splenectomy with or without chemotherapy have demonstrated favorable outcomes with a median OS exceeding 10 years and a 10-year OS rate of about 75%.[67,78] In a retrospective series of patients with splenic MZL (N=30) treated with splenectomy (followed by alkylating agent-based or anthracycline-based chemotherapy in the majority of patients) or chemotherapy alone with CHOP-like regimens and/or antiviral therapy for HCV positivity, the ORR and CR rates were 93% and 48%, respectively.[8] The median EFS was 3.3 years and the estimated 3-year OS rate was 75%.

Treatment of splenic MZL with purine analog agents (e.g., pentostatin, cladribine) alone resulted in CR rates of about 20%.[80-82] In a small phase II prospective study in patients with splenic MZL (N=16; previously treated, n=13), single-agent therapy with pentostatin induced an ORR of 68% with a CR in 23% of patients; after a median follow up of 35 months, the median PFS and OS was 18 months and 40 months,

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respectively.[81] In a retrospective analysis of patients with splenic MZL (N=50), the subgroup of patients treated with cladribine alone (n=12) had a CR rate of 21%, with a 4-year PFS rate of 52%.[80] In another retrospective study in patients with splenic MZL (N=70), the patients treated with chemotherapy alone (n=11; purine analog regimens, n=10) had a CR rate of 18%, and a 3-year FFS rate of 45%; the 3-year OS rate was 55%.[82]

The anti-CD20 monoclonal antibody rituximab has also been evaluated as both monotherapy and in combination with chemotherapy in patients with splenic MZL. In retrospective series, rituximab alone (with or without maintenance rituximab) has shown high response rates (ORR 90% to 100%; CR/CRu rates 40% to 85%) with durable remissions.[82-84] In a retrospective series of patients with splenic MZL who received rituximab alone (n=26), the ORR and CR/CRu rates were 88% and 42%, respectively.[82] The 3-year FFS and OS rates were 86% and 95%, respectively. Combination therapy with rituximab and chemotherapy appears to provide benefits over purine analog therapy alone. In a small subgroup of patients who received rituximab combined with chemotherapy (n=6), the CR/CRu rate was 33% and both the 3-year FFS and OS rates were 100%.[82] A retrospective study compared outcomes of patients with splenic MZL treated with cladribine alone (n=12) versus cladribine with rituximab (n=38).[80] The combination regimen of cladribine and rituximab resulted in significantly higher CR rate (62.5% vs. 21%; P=0.004) and 4-year PFS rate (83% vs. 52%; P=0.04) compared with cladribine alone. After a median follow up of 45 months, the 4-year PFS rate for all patients was 67% and the estimated 6-year OS rate was 89%.[80] In a recent retrospective study that assessed treatment with rituximab in patients with splenic MZL (N=43), rituximab alone or in combination resulted in an ORR of 100% with a CR in 79% of patients.[85] This CR rate compared favorably to the 30%

CR observed in patients treated with chemotherapy alone (n=10). Moreover, single-agent rituximab resulted in similar CR rates compared with rituximab-based combination (90% vs. 79%), and was associated with less toxicity. The 3-year DFS was more favorable with rituximab-containing therapy (79%) compared with splenectomy alone (29%) or chemotherapy alone (25%). The 3-year OS with rituximab was 98%.[85]

NCCN Recommendations
Asymptomatic patients with no splenomegaly or progressive cytopenia can be observed until indications for treatment develop. Patients presenting with splenomegaly should be treated depending on their HCV serology status. Hepatology evaluation is recommended for patients with HCV positivity. For patients without contradictions for treatment of hepatitis, appropriate treatment with antiviral therapy should be initiated. In addition, patients requiring treatment for symptomatic splenomegaly can be further managed with splenectomy or rituximab therapy. Patients with contraindications should be managed as described below for patients with HCV-negative disease.

Patients who are HCV-negative can be observed if they are asymptomatic. Patients who are symptomatic (cytopenias or symptoms of splenomegaly, weight loss, early satiety or abdominal pain) should be treated with splenectomy or rituximab. Pneumococcal and meningococcal vaccination should be given at least 2 weeks before splenectomy. Patients should be monitored on a regular basis following treatment. Clinical follow up (including repeat diagnostic tests and imaging studies, as clinically indicated) should be performed every 3-6 months for 5 years and then annually or as clinically indicated thereafter. Patients with evidence of disease progression should be managed according to the recommendations for advanced-stage FL in the NCCN Guidelines.

References

1. Kahl B, Yang D. Marginal zone lymphomas: management of nodal, splenic, and MALT NHL. Hematology Am Soc Hematol Educ Program 2008:359-364. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/19074110.

2. Thieblemont C. Clinical presentation and management of marginal zone lymphomas. Hematology Am Soc Hematol Educ Program 2005:307-313. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/16304396.

3. Campo E, Pileri SA, Jaffe ES, et al. Nodal marginal zone lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:218-219.

4. Isaacson PG, Chott A, Nakamura S, et al. Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). In: Swerdlow SH, Campo E, Harris NL, et al. eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:214-217. Available at:

5. Isaacson PG, Thieblemont C, Piris MA, et al. Splenic B-cell marginal zone lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:185-187.

6. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 1997;89:3909-3918. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9166827.

7. Olszewski AJ, Castillo JJ. Survival of patients with marginal zone lymphoma: Analysis of the Surveillance, Epidemiology, and End Results database. Cancer 2012. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/22893605.

8. Arcaini L, Paulli M, Boveri E, et al. Splenic and nodal marginal zone lymphomas are indolent disorders at high hepatitis C virus seroprevalence with distinct presenting features but similar morphologic and phenotypic profiles. Cancer 2004;100:107-115. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/14692030.

9. Mele A, Pulsoni A, Bianco E, et al. Hepatitis C virus and B-cell non-Hodgkin lymphomas: an Italian multicenter case-control study. Blood 2003;102:996-999. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/12714514.

10. Arcaini L, Burcheri S, Rossi A, et al. Prevalence of HCV infection in nongastric marginal zone B-cell lymphoma of MALT. Ann Oncol 2007;18:346-350. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/17071937.

11. Berger F, Traverse-Glehen A, Felman P, et al. Clinicopathologic features of Waldenstrom's macroglobulinemia and marginal zone lymphoma: are they distinct or the same entity? Clin Lymphoma 2005;5:220-224. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/15794852.

12. Treon SP, Xu L, Yang G, et al. MYD88 L265P somatic mutation in Waldenstrom's macroglobulinemia. N Engl J Med 2012;367:826-833. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22931316.

13. Gachard N, Parrens M, Soubeyran I, et al. IGHV gene features and MYD88 L265P mutation separate the three marginal zone lymphoma entities and Waldenstrom macroglobulinemia/lymphoplasmacytic lymphomas. Leukemia 2013;27:183-189. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/22944768.

14. Varettoni M, Arcaini L, Zibellini S, et al. Prevalence and clinical significance of the MYD88 (L265P) somatic mutation in Waldenstrom's macroglobulinemia and related lymphoid neoplasms. Blood 2013;121:2522-2528. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/23355535.

15. Nathwani BN, Anderson JR, Armitage JO, et al. Marginal zone B-cell lymphoma: A clinical comparison of nodal and mucosa-associated lymphoid tissue types. Non-Hodgkin's Lymphoma Classification Project. J Clin Oncol 1999;17:2486-2492. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10561313.

16. Thieblemont C, Bastion Y, Berger F, et al. Mucosa-associated lymphoid tissue gastrointestinal and nongastrointestinal lymphoma behavior: analysis of 108 patients. J Clin Oncol 1997;15:1624-1630. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9193362.

17. Zucca E, Conconi A, Pedrinis E, et al. Nongastric marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. Blood 2003;101:2489-2495. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12456507.

18. Ueda K, Terui Y, Yokoyama M, et al. Non-gastric advanced mucosa-associated lymphoid tissue (MALT) lymphoma has worse prognosis than gastric MALT lymphoma even when treated with rituximab-containing chemotherapy. Leuk Lymphoma 2013;54 1928-1933. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23216271.

19. Thieblemont C, Berger F, Dumontet C, et al. Mucosa-associated lymphoid tissue lymphoma is a disseminated disease in one third of 158 patients analyzed. Blood 2000;95:802-806. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10648389.

20. Farinha P, Gascoyne RD. Molecular pathogenesis of mucosa-associated lymphoid tissue lymphoma. J Clin Oncol 2005;23:6370-6378. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16155022.

21. Auer IA, Gascoyne RD, Connors JM, et al. t(11;18)(q21;q21) is the most common translocation in MALT lymphomas. Ann Oncol 1997;8:979-985. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9402171.

22. Murga Penas EM, Hinz K, Roser K, et al. Translocations t(11;18)(q21;q21) and t(14;18)(q32;q21) are the main chromosomal abnormalities involving MLT/MALT1 in MALT lymphomas. Leukemia 2003;17:2225-2229. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12931213.

23. Willis TG, Jadayel DM, Du MQ, et al. Bcl10 is involved in t(1;14)(p22;q32) of MALT B cell lymphoma and mutated in multiple tumor types. Cell 1999;96:35-45. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9989495.

24. Liu H, Ye H, Dogan A, et al. T(11;18)(q21;q21) is associated with advanced mucosa-associated lymphoid tissue lymphoma that expresses nuclear BCL10. Blood 2001;98:1182-1187. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11493468.

25. Streubel B, Lamprecht A, Dierlamm J, et al. T(14;18)(q32;q21) involving IGH and MALT1 is a frequent chromosomal aberration in MALT lymphoma. Blood 2003;101:2335-2339. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12406890.

26. Streubel B, Vinatzer U, Lamprecht A, et al. T(3;14)(p14.1;q32) involving IGH and FOXP1 is a novel recurrent chromosomal aberration in MALT lymphoma. Leukemia 2005;19:652-658. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15703784.

27. Wotherspoon AC. Gastric lymphoma of mucosa-associated lymphoid tissue and Helicobacter pylori. Annu Rev Med 1998;49:289-299. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9509264.

28. Isaacson PG, Spencer J. Gastric lymphoma and Helicobacter pylori. Important Adv Oncol 1996:111-121. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8791131.

29. Ye H, Liu H, Raderer M, et al. High incidence of t(11;18)(q21;q21) in Helicobacter pylori-negative gastric MALT lymphoma. Blood 2003;101:2547-2550. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12517817.

30. Liu H, Ye H, Ruskone-Fourmestraux A, et al. T(11;18) is a marker for all stage gastric MALT lymphomas that will not respond to H. pylori eradication. Gastroenterology 2002;122:1286-1294. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11984515.

31. Morgner A, Bayerdorffer E, Neubauer A, Stolte M. Helicobacter pylori associated gastric B cell MALT lymphoma: predictive factors for regression. Gut 2001;48:290-292. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11171813.

32. Pavlick AC, Gerdes H, Portlock CS. Endoscopic ultrasound in the evaluation of gastric small lymphocytic mucosa-associated lymphoid tumors. J Clin Oncol 1997;15:1761-1766. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9164183.

33. Sackmann M, Morgner A, Rudolph B, et al. Regression of gastric MALT lymphoma after eradication of Helicobacter pylori is predicted by endosonographic staging. MALT Lymphoma Study Group. Gastroenterology 1997;113:1087-1090. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9322502.

34. Nakamura S, Matsumoto T, Suekane H, et al. Predictive value of endoscopic ultrasonography for regression of gastric low grade and high grade MALT lymphomas after eradication of Helicobacter pylori. Gut 2001;48:454-460. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11247887.

35. Rohatiner A, d'Amore F, Coiffier B, et al. Report on a workshop convened to discuss the pathological and staging classifications of gastrointestinal tract lymphoma. Ann Oncol 1994;5:397-400. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8075046.

36. Stathis A, Chini C, Bertoni F, et al. Long-term outcome following Helicobacter pylori eradication in a retrospective study of 105 patients with localized gastric marginal zone B-cell lymphoma of MALT type. Ann Oncol 2009;20:1086-1093. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19193705.

37. Steinbach G, Ford R, Glober G, et al. Antibiotic treatment of gastric lymphoma of mucosa-associated lymphoid tissue. An uncontrolled trial. Ann Intern Med 1999;131:88-95. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10419446.

38. Wundisch T, Thiede C, Morgner A, et al. Long-term follow-up of gastric MALT lymphoma after Helicobacter pylori eradication. J Clin Oncol 2005;23:8018-8024. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16204012.

39. Chen L, Lin J, Tai J, et al. Long-term results of anti-Helicobacter pylori therapy in early-stage gastric high-grade transformed MALT lymphoma. J Natl Cancer Inst 2005;97:1345-1353. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16174856.

40. Andriani A, Miedico A, Tedeschi L, et al. Management and long-term follow-up of early stage H. pylori-associated gastric MALT-lymphoma in clinical practice: an Italian, multicentre study. Dig Liver Dis 2009;41:467-473. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18945654.

41. Montalban C, Santon A, Boixeda D, et al. Treatment of low grade gastric mucosa-associated lymphoid tissue lymphoma in stage I with Helicobacter pylori eradication. Long-term results after sequential histologic and molecular follow-up. Haematologica 2001;86:609-617. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11418369.

42. Nakamura S, Matsumoto T, Suekane H, et al. Long-term clinical outcome of Helicobacter pylori eradication for gastric mucosa-associated lymphoid tissue lymphoma with a reference to second-line treatment. Cancer 2005;104:532-540. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15937928.

43. Wotherspoon AC, Doglioni C, Diss TC, et al. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of Helicobacter pylori. Lancet 1993;342:575-577. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8102719.

44. Tsang RW, Gospodarowicz MK, Pintilie M, et al. Localized mucosa-associated lymphoid tissue lymphoma treated with radiation therapy has excellent clinical outcome. J Clin Oncol 2003;21:4157-4164. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14615444.

45. Goda JS, Gospodarowicz M, Pintilie M, et al. Long-term outcome in localized extranodal mucosa-associated lymphoid tissue lymphomas treated with radiotherapy. Cancer 2010;116:3815-3824. Available at: http://www.ncbi.nlm.nih.gov/PubMed/20564130.

46. Vrieling C, de Jong D, Boot H, et al. Long-term results of stomach-conserving therapy in gastric MALT lymphoma. Radiother Oncol 2008;87:405-411. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18343513.

47. Aviles A, Nambo MJ, Neri N, et al. Mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach: results of a controlled clinical trial. Med Oncol 2005;22:57-62. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15750197.

48. Koch P, Probst A, Berdel WE, et al. Treatment results in localized primary gastric lymphoma: data of patients registered within the German multicenter study (GIT NHL 02/96). J Clin Oncol 2005;23:7050-7059. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16129843.

49. Schechter NR, Portlock CS, Yahalom J. Treatment of mucosa-associated lymphoid tissue lymphoma of the stomach with radiation alone. J Clin Oncol 1998;16:1916-1921. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9586910.

50. Martinelli G, Laszlo D, Ferreri AJM, et al. Clinical activity of rituximab in gastric marginal zone non-Hodgkin's lymphoma resistant to or not eligible for anti-Helicobacter pylori therapy. J Clin Oncol 2005;23:1979-1983. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15668468.

51. Hammel P, Haioun C, Chaumette MT, et al. Efficacy of single-agent chemotherapy in low-grade B-cell mucosa-associated lymphoid tissue lymphoma with prominent gastric expression. J Clin Oncol 1995;13:2524-2529. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7595703.

52. Jager G, Neumeister P, Brezinschek R, et al. Treatment of extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type with cladribine: a phase II study. J Clin Oncol 2002;20:3872-3877. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12228207.

53. Jager G, Neumeister P, Quehenberger F, et al. Prolonged clinical remission in patients with extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue type treated with cladribine: 6 year follow-up of a phase II trial. Ann Oncol 2006;17:1722-1723. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16766585.

54. Wohrer S, Drach J, Hejna M, et al. Treatment of extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) with mitoxantrone, chlorambucil and prednisone (MCP). Ann Oncol 2003;14:1758-1761. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14630681.

55. Raderer M, Wohrer S, Streubel B, et al. Activity of rituximab plus cyclophosphamide, doxorubicin/mitoxantrone, vincristine and prednisone in patients with relapsed MALT lymphoma. Oncology 2006;70:411-417. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17220639.

56. Salar A, Domingo-Domenech E, Estany C, et al. Combination therapy with rituximab and intravenous or oral fludarabine in the first-line, systemic treatment of patients with extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue type. Cancer 2009;115:5210-5217. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19672998.

57. Troch M, Kiesewetter B, Willenbacher W, et al. Rituximab plus subcutaneous cladribine in patients with extranodal marginal zone B-cell lymphoma of the mucosa associated lymphoid tissue-Lymphoma: a

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phase II study by the Arbeitsgemeinschaft Medikamentose Tumortherapie. Haematologica 2013;98:264-268. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22983582.

58. Levy M, Copie-Bergman C, Amiot A, et al. Rituximab and chlorambucil versus rituximab alone in gastric mucosa-associated lymphoid tissue lymphoma according to t(11;18) status: a monocentric non-randomized observational study. Leuk Lymphoma 2013;54:940-944. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22978684.

59. Zucca E, Conconi A, Laszlo D, et al. Addition of Rituximab to Chlorambucil Produces Superior Event-Free Survival in the Treatment of Patients With Extranodal Marginal-Zone B-Cell Lymphoma: 5-Year Analysis of the IELSG-19 Randomized Study. J Clin Oncol 2013;31:565-572. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23295789.

60. Salar A, Domingo-Domenech E, Panizo C, et al. Final Results of a Multicenter Phase II Trial with Bendamustine and Rituximab As First Line Treatment for Patients with MALT Lymphoma (MALT-2008-01) [abstract]. Blood 2012;120:Abstract 3691. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/120/21/3691.

61. Conconi A, Martinelli G, Lopez-Guillermo A, et al. Clinical activity of bortezomib in relapsed/refractory MALT lymphomas: results of a phase II study of the International Extranodal Lymphoma Study Group (IELSG). Ann Oncol 2011;22:689-695. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20810546.

62. Hancock BW, Qian W, Linch D, et al. Chlorambucil versus observation after anti-Helicobacter therapy in gastric MALT lymphomas: results of the international randomised LY03 trial. Br J Haematol 2009;144:367-375. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19036078.

63. Zucca E, Dreyling M. Gastric marginal zone lymphoma of MALT type: ESMO Clinical Practice Guidelines for diagnosis, treatment and

follow-up. Ann Oncol 2010;21 Suppl 5:v175-176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20555074.

64. Arcaini L, Burcheri S, Rossi A, et al. Nongastric marginal-zone B-cell MALT lymphoma: prognostic value of disease dissemination. Oncologist 2006;11:285-291. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16549813.

65. Conconi A, Martinelli G, Thieblemont C, et al. Clinical activity of rituximab in extranodal marginal zone B-cell lymphoma of MALT type. Blood 2003;102:2741-2745. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12842999.

66. Berger F, Felman P, Thieblemont C, et al. Non-MALT marginal zone B-cell lymphomas: a description of clinical presentation and outcome in 124 patients. Blood 2000;95:1950-1956. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10706860.

67. Thieblemont C, Felman P, Berger F, et al. Treatment of splenic marginal zone B-cell lymphoma: an analysis of 81 patients. Clin Lymphoma 2002;3:41-47. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12141954.

68. Franco V, Florena AM, Iannitto E. Splenic marginal zone lymphoma. Blood 2003;101:2464-2472. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12446449.

69. Blombery P, Wong SQ, Hewitt CA, et al. Detection of BRAF mutations in patients with hairy cell leukemia and related lymphoproliferative disorders. Haematologica 2012;97:780-783. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22133769.

70. Arcaini L, Zibellini S, Boveri E, et al. The BRAF V600E mutation in hairy cell leukemia and other mature B-cell neoplasms. Blood 2012;119:188-191. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22072557.

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NCCN Guidelines Version 4.2014
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71. Xu L, Hunter ZR, Yang G, et al. MYD88 L265P in Waldenstrom macroglobulinemia, immunoglobulin M monoclonal gammopathy, and other B-cell lymphoproliferative disorders using conventional and quantitative allele-specific polymerase chain reaction. Blood 2013;121:2051-2058. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23321251.

72. Weng WK, Levy S. Hepatitis C virus (HCV) and lymphomagenesis. Leuk Lymphoma 2003;44:1113-1120. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12916862.

73. Hermine O, Lefrere F, Bronowicki JP, et al. Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection. N Engl J Med 2002;347:89-94. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12110736.

74. Kelaidi C, Rollot F, Park S, et al. Response to antiviral treatment in hepatitis C virus-associated marginal zone lymphomas. Leukemia 2004;18:1711-1716. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15284859.

75. Vallisa D, Bernuzzi P, Arcaini L, et al. Role of anti-hepatitis C virus (HCV) treatment in HCV-related, low-grade, B-cell, non-Hodgkin's lymphoma: a multicenter Italian experience. J Clin Oncol 2005;23:468-473. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15659492.

76. Arcaini L, Vallisa D, Merli M, et al. Hematolgical response to antiviral treatment in 94 patients with indolent B-cell lymphomas associated with hepatitis C virus infection: a study of the Fondazione Italiana Linfomi (FIL) [abstract]. Ann Oncol 2011;22 (Suppl 4):Abstract 138. Available at: http://annonc.oxfordjournals.org/content/22/suppl_4/iv128.

77. Iannitto E, Ambrosetti A, Ammatuna E, et al. Splenic marginal zone lymphoma with or without villous lymphocytes. Hematologic findings and outcomes in a series of 57 patients. Cancer 2004;101:2050-2057. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15389479.

78. Milosevic R, Todorovic M, Balint B, et al. Splenectomy with chemotherapy vs surgery alone as initial treatment for splenic marginal zone lymphoma. World J Gastroenterol 2009;15:4009-4015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19705496.

79. Chacon JI, Mollejo M, Munoz E, et al. Splenic marginal zone lymphoma: clinical characteristics and prognostic factors in a series of 60 patients. Blood 2002;100:1648-1654. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12176884.

80. Cervetti G, Galimberti S, Sordi E, et al. Significant efficacy of 2-CdA with or without rituximab in the treatment of splenic marginal zone lymphoma (SMZL). Ann Oncol 2010;21:851-854. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19825880.

81. Iannitto E, Minardi V, Calvaruso G, et al. Deoxycoformycin (pentostatin) in the treatment of splenic marginal zone lymphoma (SMZL) with or without villous lymphocytes. Eur J Haematol 2005;75:130-135. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16000129.

82. Tsimberidou AM, Catovsky D, Schlette E, et al. Outcomes in patients with splenic marginal zone lymphoma and marginal zone lymphoma treated with rituximab with or without chemotherapy or chemotherapy alone. Cancer 2006;107:125-135. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16700034.

83. Bennett M, Sharma K, Yegena S, et al. Rituximab monotherapy for splenic marginal zone lymphoma. Haematologica 2005;90:856-858. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15951303.

84. Kalpadakis C, Pangalis GA, Dimopoulou MN, et al. Rituximab monotherapy is highly effective in splenic marginal zone lymphoma. Hematol Oncol 2007;25:127-131. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17514771.

85. Else M, Marin-Niebla A, de la Cruz F, et al. Rituximab, used alone or in combination, is superior to other treatment modalities in splenic

marginal zone lymphoma. Br J Haematol 2012;159:322-328. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23016878.

Mantle Cell Lymphoma

Diagnosis

Mantle cell lymphoma (MCL) comprises about 6% of all newly diagnosed cases of NHL.[1] MCL can be readily distinguished from other small lymphocytic lymphomas due to the widespread availability of appropriated diagnostic reagents.[2] The diagnosis can be established by histological examination in combination with immunohistochemistry (IHC) with a profile consisting of CD5+, CD10-/+, CD20+, CD23-/+, CD43+, and cyclin D1+. Some cases of MCL may be CD5- or CD23+. MCL is characterized by the reciprocal chromosomal translocation t(11;14), resulting in the overexpression of cyclin D1 and the diagnosis of MCL generally requires the expression of cyclin D1.[3] However, cyclin D1-negative MCL cases with otherwise typical immunophenotype can be observed, though rare (<5% of cases).[4,5] Recent gene expression profiling data suggest that cyclin D1 expression may not be required for the molecular signature of MCL; in these rare cases of MCL negative for cyclin D1 and t(11;14), over-expression of cyclin D2 or cyclin D3 may be observed.[6,7] IHC for cyclin D2 or cyclin D3 is not helpful in establishing the diagnosis of cyclin D1-negative MCL as these proteins are also expressed in other B-cell malignancies. A recent study of cyclin D1-negative MCL showed rearrangements involving the *CCND2* gene in 55% of cases, which was associated with high expression of cyclin D2 mRNA.[8] Gene expression and miRNA profiling showed that the genomic signatures of cyclin D1-negative MCL cases were similar to those of cyclin D1-positive cases.[5,6,8] Nuclear overexpression of the transcription factor SOX11 is observed in nearly all cases of MCL, regardless of cyclin D1 expression level, and may potentially aid in differentiating cyclin D1-negative MCL cases from other B-cell lymphomas.[9-11] The pathologic features and clinical characteristics of cyclin D1-negative MCL appear to be similar to those of cyclin D1-positive cases.[6,8] Thus, in the absence of data suggesting otherwise,

cases of cyclin D1-negative MCL should not be managed differently than cyclin D1-positive cases.

Currently available reagents for IHC evaluation of cyclin D1 are robust and yield good staining; however, in some cases, molecular analysis of *CCND1* rearrangements or cytogenetics or FISH for the translocation t(11;14), juxtaposing the cyclin D1 locus with the IgH locus, can be helpful for diagnosis.[12] In certain cases, cytogenetics or FISH for t(14;18) and a FISH panel for chronic lymphocytic leukemia (CLL) may also be useful. In addition, Ki-67 should be included in the IHC panel for initial diagnostic workup. Ki-67 proliferation index of less than 30% has been associated with a more favorable prognosis.[13-17] However, this should not be used to guide treatment decisions at this time.

In-Situ Involvement of Mantle Cell Lymphoma-like Cells of Unknown Significance (Mantle Cell Lymphoma "In Situ")

The presence of MCL-like B-cells in the mantle zones of morphologically reactive lymph nodes ("MCL in situ") has been described in several case reports (including in patients with lymphoid hyperplasia).[18,19] Cases of "MCL in situ" have been characterized by preservation of the lymph node architecture and presence of cyclin D1-positive B-cells restricted to the mantle zones with minimal expansion of the mantle zone (and with only minimal or no spread of cyclin D1-positive cells in the interfollicular area).[18-21] More recently, an unusual case of "MCL in situ" was reported that showed a scattering of cyclin D1-positive cells in the germinal centers (but not the mantle zones) of a lymph node specimen retrospectively evaluated several years prior to the diagnosis of symptomatic MCL.[22]

The occurrence of "MCL in situ" in studies of reactive lymph nodes was very rare.[20,23] In an analysis of a consecutive series of unselected surgical samples of reactive lymph nodes from patients without a history

of lymphoma (n=131; 1292 samples), no cases of "MCL in situ" were identified.[23] Development of overt MCL in patients found to have "MCL in situ" has been reported, although this appears to be very uncommon.[20] The significance or potential for malignancy of "MCL in situ" in patients without known MCL remains uncertain. These cases appear to have a very indolent course with long-term survival even without treatment intervention.[20,21] It is therefore important to distinguish cases of "MCL in situ" from cases of overt MCL with a mantle zone pattern. In patients with the former in whom overt MCL can be excluded based on a thorough evaluation (e.g., biopsy of additional suspicious nodes, physical examination, peripheral blood flow cytometry, CT scan of neck, chest, abdomen, and pelvis) close follow-up may still be warranted.[24] Similar to "follicular lymphoma in situ", the WHO classification recommends that a diagnosis of MCL not be made in such cases.

Workup

The workup for MCL is similar to the workup for many indolent lymphomas and certain aggressive lymphomas. The initial workup for newly diagnosed MCL should include a thorough physical examination with attention to node-bearing areas, and evaluation of performance status and constitutional symptoms. Laboratory assessments should include standard blood work including CBC with differential and a comprehensive metabolic panel, in addition to measurements of serum lactate dehydrogenase (LDH). Patients with high tumor burden and elevated LDH should be assessed for spontaneous tumor lysis syndrome, including measurements of uric acid level. Measurement of serum beta-2-microglobulin levels may also be useful in some circumstances. HBV testing is recommended due to increased risks of viral reactivation when immunotherapy regimens are being considered for treatment. MCL is a systemic disease with frequent involvement of

the bone marrow, gastrointestinal (GI) tract and may also present with a leukemic phase. For this reason, both the peripheral blood and bone marrow must be carefully evaluated for the presence of malignant cells. Adequate trephine biopsy should be obtained for initial staging evaluation, with or without bone marrow aspiration. Chest, abdominal, and pelvic CT scans are routinely performed. PET-CT scan and CT scan of the neck may be helpful in selected cases. In patients with the blastic variant or for patients presenting with CNS symptoms, a lumbar puncture should be performed to evaluate the cerebral spinal fluid for potential disease involvement.

GI involvement has been reported in 15% to 30% of patients with MCL. In two prospective studies, the frequency of GI tract involvement in patients with MCL was higher than that reported in the literature.[25,26] Salar et al reported upper or lower GI tract involvement in 92% of patients at diagnosis. In the study by Romaguera et al., MCL was histologically present in the lower and upper GI tract in 88% and 43% of patients, respectively.[25] In this report, 26% of patients presented with GI symptoms at the time of diagnosis. Despite the high frequency of GI tract involvement (which was primarily observed at the microscopic level), the use of endoscopy with biopsies led to changes in clinical management in only 4% of patients.[25] The NCCN Guidelines panel does not recommend endoscopy or colonoscopy as part of routine initial workup, but suggests that it may be useful in certain circumstances. However, endoscopic or colonoscopic evaluation of the GI tract is necessary for confirmation of stage I-II disease and for response assessment to initial therapy.

Treatment Options based on Clinical Stage

Generally, MCL is thought to possess the worst characteristics of both indolent and aggressive NHL subtypes owing to the incurability of

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disease with conventional chemotherapy and a more aggressive disease course.[27]

Stage I-II

Few patients present with localized MCL and the available published literature on management is retrospective and anecdotal. In a retrospective analysis of patients with limited bulk, early-stage (stage IA or IIA) MCL (n=26), inclusion of RT with or without chemotherapy was associated with significantly improved progression-free survival (PFS) at 5 years (68% vs. 11%; P =.002) and a trend towards improved overall survival (OS).[28]

Stage II (bulky) and Stage III-IV

Several regimens have shown significant activity in newly diagnosed patients with MCL, but none of these regimens are curative in patients with advanced disease.

In a database analysis from a single-center cohort (n=111), Martin et al reported that treatment with regimens including R-CHOP or R-CVP could yield survival outcomes similar to that achieved with more intensive approaches.[29] The median OS from diagnosis was 85 months, and the 5-year OS rate was 66%. Among patients with available data on treatment regimens (n=75), the majority (70%) had received CHOP-like therapy with or without rituximab, with only 7% having received more intensive first-line therapies (R-hyper-CVAD and/or high-dose therapy with autologous stem cell rescue [HDT/ASCR]).[29]

However, a more recently published analysis from the NCCN Oncology Outcomes Database suggested that median PFS remained 3-4 years despite the use of aggressive regimens in patients with MCL (n=167).[30] This analysis reported superior PFS outcomes with R-hyper-CVAD alone or with rituximab-containing regimens (e.g., R-CHOP) followed by

HDT/ASCT, compared with R-CHOP alone, in the first-line setting for younger patients (<65 years of age) with MCL.[30]

Aggressive First-Line Therapy

Rituximab used in combination with hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; alternating with high-dose methotrexate and cytarabine) [R-hyper-CVAD] has resulted in favorable PFS and OS outcomes.[31-34]

In a phase II study in previously untreated patients with MCL (n=97), R-hyper-CVAD produced 3-year failure-free survival (FFS) and OS rates of 64% and 82%, respectively, with a median follow-up time of 40 months.[31] After 10 years of follow-up, the median OS had not been reached and the median time to failure (TTF) was 4.6 years for all patients. Among patients 65 years or younger, the median OS had not been reached and the median TTF was 5.9 years. In the multivariate analysis pre-treatment serum levels of beta-2- microglobulin, IPI score and MIPI score were predictive of both OS and TTF.[32] FFS and OS rates were 43% and 60%, respectively; among patients 65 years or younger, the corresponding survival rates were 52% and 68%, respectively.

In the Italian study (60 evaluable patients), R-hyper-CVAD resulted in an overall response rate of 83% with a CR rate of 72%. The 5-year PFS and OS rates were 61% and 73%, respectively.[33] However, this regimen was associated with substantial toxicity.

In the SWOG 0213 study, R-hyper-CVAD induced CR/CRu in 58% of previously untreated patients (age <70 years) with MCL (n=49).[34] With a median follow-up of 4.8 years, the median PFS and OS was 4.8 years (5.5 years for those ≤ 65 years) and 6.8 years respectively. The 2-year PFS and OS rates were 63% and 76%, respectively.

Less Aggressive First-Line Therapy
In the earlier studies, the addition of rituximab to CHOP chemotherapy was associated with high response rates but did not translate to prolonged PFS or OS.[35,36] A phase III randomized trial in the German Low Grade Lymphoma study group evaluated R CHOP versus CHOP alone in previously untreated patients (age ≤65 years) with advanced stage MCL (n=122).[36] In this study, R CHOP was significantly superior to CHOP in terms of ORR (94% vs. 75%), CR rate (34% vs 7%) and median time to treatment failure (21 months vs. 14 months). However, no differences were observed between treatment arms for PFS or OS outcomes.[36]

Other non-aggressive regimens have also been evaluated in clinical trials. The combination of bendamustine with rituximab (BR regimen) was investigated in a randomized phase III study of the StiL (Study Group Indolent Lymphomas), which compared BR versus R-CHOP as first-line therapy in patients with advanced follicular, indolent, and mantle cell lymphomas (514 evaluable patients; MCL histology comprised 18% of patients).[37] The ORR was similar in both arms (93% with BR vs. 91% with R-CHOP), although the CR rate was significantly higher in the BR arm (40% vs. 30%; P =.021). With a median follow-up time of 45 months, the BR arm was associated with significantly longer median PFS (primary endpoint) compared with R-CHOP (69.5 months vs. 31.2 months; HR=0.58, 95% CI 0.44–0.74; P <.0001); however. OS outcomes were not significantly different between treatment arms. Among the subgroup of patients with MCL histology, median PFS was also significantly higher with BR compared with R-CHOP (35 months vs. 22 months; HR=0.49, 95% CI 0.28–0.79; P =.0044).[37] The BR regimen was associated with less frequent serious adverse events (19% vs. 29%) and less grade 3-4 hematologic toxicities compared with R-CHOP. Grade 3-4 neutropenia was reported in 29% in the BR arm

and 69% with R-CHOP. Peripheral neuropathy (all grades) was less frequent in the BR arm (7% vs. 29%). Infectious complications (all grades) were also less frequent with BR compared with R-CHOP (37% vs. 50%). Fatal sepsis occurred in 1 patient in the BR arm and 5 patients in the R-CHOP arm. The BR regimen was more frequently associated with skin toxicities (all grades) including erythema (16% vs. 9%) and allergic reactions (15% vs. 6%) compared with R-CHOP.[37] Although this phase III randomized trial showed superior PFS outcomes with the BR regimen compared with R-CHOP, there may be limitations given that data from more than half of the patients in this trial were censored prior to the minimum follow-up period.

The combination of bendamustine and rituximab with the addition of cytarabine was evaluated in a phase II study in older patients with MCL (age ≥ 65 years; not eligible for intensive regimens or HDT/ASCR).[38] Among enrolled patients (n=40; median age 70 years), 50% were previously untreated, 93% had stage III/IV disease and 49% had high-risk MIPI scores. Patients with relapsed/refractory disease (n=20) had all previously received rituximab-containing therapies.[38] Among previously untreated patients, the ORR was 100% and the 2-year PFS rate was 95%. Among relapsed/refractory patients, the ORR was 70% and the 2-year PFS was 70%. The most common grade 3 or 4 toxicities included transient thrombocytopenia (87%) and febrile neutropenia (12%).[38]

Cladribine, alone or in combination with rituximab, has shown activity in patients with previously untreated MCL.[39-41] In trials conducted by the North Central Cancer Treatment group, the ORR and median PFS for single agent cladribine were 81% (42% CR) and 14 months, respectively, for previously untreated patients (n=26); the combination of cladribine and rituximab as initial therapy (n=29) resulted in an ORR of 66% (52% CR) and median PFS of 12 months.[39] In a small trial in

patients with previously untreated and pretreated MCL (n=12), cladribine alone induced an ORR of 58% (25% CR) with a median time to progression of 19 months.[40] In a recent retrospective study in patients with previously untreated MCL (n=31), cladribine combined with rituximab yielded an ORR of 87% (61% CR/CRu) with a median PFS and OS of 37.5 months and 85 months, respectively.[41] It should be noted that in this study, the majority of responding patients had received post-induction maintenance therapy with rituximab.

First-Line Consolidation Therapy
HDT/ASCR as first-line consolidation has demonstrated promising outcomes in a number of studies.[42-48]

In a prospective study of sequential frontline CHOP/DHAP followed by HDT/ASCR in patients with MCL (n=28; n=23 proceeded to transplant), the 3-year event-free survival (EFS) and OS rates were 83% and 90%, respectively.[44] Median OS was not reached after a median follow up of almost 48 months. In a randomized trial conducted by the European MCL Network, patients (age ≤65 years) with advanced stage MCL (n=122) in remission after CHOP-like chemotherapy were randomized to HDT/ASCR or maintenance with interferon alfa.[45] In this study, HDT/ASCR was associated with a significantly longer median PFS compared with interferon alfa maintenance (39 months vs. 17 months; P=0.011) The 3-year OS rates were 83% and 77%, respectively, and were not significantly different between consolidation arms.[45]

In a study conducted by the MD Anderson Cancer Center, HDT/ASCR in patients with MCL (n=33) in first remission following treatment with hyper-CVAD resulted in 5-year disease-free survival and OS rates of 42% and 77%, respectively.[43] In particular, the subgroup of patients with low serum beta-2 microglobulin levels appeared to benefit most, with a 5-year OS rate of 100% (compared with 22% for patients with elevated

beta-2 microglobulin).[43] In an analysis of long-term outcomes from patients with MCL treated at the MD Anderson Cancer Center (including the 33 patients reported in the earlier study above), the subgroup of patients treated primarily with hyper-CVAD (with or without rituximab) followed by HDT/ASCR in first remission (n=50) showed a median PFS of 42 months and a median OS of 93 months.[47]

In a small prospective study that evaluated R-hyper-CVAD followed by HDT/ASCR in patients with previously untreated MCL (n=13; 12 patients proceeded to transplant), the 3-year EFS and OS rate was 92% for both endpoints.[46] These results with R-hyper-CVAD appear favorable relative to induction with R-CHOP.

In a phase II study that evaluated R-CHOP induction followed by HDT/ASCR in patients with previously untreated MCL (n=87; 61 patients proceeded to transplant), the 4-year failure-free survival and OS rates were 36% and 66%, respectively.[48]

In another study, patients with MCL treated with hyper-CVAD or CHOP (with or without rituximab, in either regimen) followed by HDT/ASCR in first remission (n=36) had 3-year PFS and OS rates of 63% and 93%, respectively.[49] Induction with hyper-CVAD resulted in a higher 3-year PFS rate compared with CHOP (81% vs. 44%), although the difference was not statistically significant. The 3-year OS rate was similar between induction regimens (94% vs. 92%, respectively).[49] Disease status at transplant was the most significant factor affecting survival following HDT/ASCR.[49,50] Patients in first remission (CR or PR) at the time of transplant had improved survival outcomes compared with those with relapsed or refractory disease. As mentioned above, among patients transplanted in first remission, hyper-CVAD (with or without rituximab) induction was associated with an improved PFS outcome compared with CHOP (with or without rituximab) in non-randomized studies.[49]

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Several different induction regimens incorporating rituximab in combination with dose intensified anthracycline-based[16,51,52] or cladribine-based chemotherapy[53-55] followed by HDT/ASCR have shown promising efficacy in relatively young newly diagnosed patients with MCL.

In the Nordic MCL trial, induction therapy with rituximab and dose intensified CHOP (maxi-CHOP) alternating with high-dose cytarabine resulted in an ORR and CR rate of 96% and 54%, respectively, in previously untreated patients (age ≤65 years) with MCL (n=160).[51] Responding patients were eligible to proceed with HDT/ASCR. The 6-year PFS and OS rates were 66% and 70%, respectively, with no relapses occurring after a median follow up of approximately 4 years (at the time of the initial report).[51] Further follow up from this study with a median observation time of 6.5 years showed median EFS of 7.4 years; median OS exceeded 10 years.[56] Late relapses were reported in 6 patients, who experienced disease progression more than 5 years after the end of therapy. In the multivariate analysis from this study, the international MCL Prognostic Index (MIPI) and ki-67 expression level were the only independent predictors of survival outcomes.[56] However, in this trial, patients were monitored by disease-specific primers for molecular relapse (MRD), and those who relapsed received rituximab as re-induction but were not considered to have relapsed unless there was morphologic evidence of relapse.

The Cancer and Leukemia Group B (CALGB 59909 trial) reported that rituximab in combination with methotrexate and augmented CHOP followed by HDT/ASCR was safe and effective in patients with newly diagnosed MCL (n=78).[52] At a median follow-up of 4.7 years, the 5-year PFS and OS rates were 56% and 64%, respectively.[52]

In newly diagnosed patients with MCL (n=88 evaluable), sequential chemotherapy (CHOP followed by ICE) with or without rituximab followed by consolidation with HDT/ASCR was associated with a superior PFS compared with RIT followed by CHOP (4-year PFS rate: 65% vs. 26%); the 4-year OS rate was 84% for both treatment groups.[16] This study also demonstrated the prognostic significance of the proliferation index on PFS outcomes. Moreover, among the subgroup of patients with a proliferation index <30%, HDT/ASCR resulted in superior PFS compared with RIT-CHOP (5-year PFS rate: 82% vs. 24%).[16]

In the phase III randomized Intergroup trial conducted by the European MCL Network, sequential treatment with 3 cycles each of R-CHOP and R-DHAP followed by HDT/ASCR (using high-dose cytarabine containing myeloablative regimen) induced higher remission rates compared with 6 cycles of R-CHOP followed by HDT/ASCR (using myeloablative radiochemotherapy) in patients (age ≤ 65 years) with advanced stage MCL (391 evaluable patients).[53] The clinical CR rate was 39% and 26%, respectively; median time to treatment failure (TTF) was not reached in the R-CHOP/R-DHAP arm compared with 49 months in the R-CHOP arm, after a median follow up of 27 months. The rate of molecular remission (MRD-negative status in peripheral blood or bone marrow) was significantly higher in the R-CHOP/R-DHAP arm compared with R-CHOP (73% vs. 32%). Achievement of molecular remission in the bone marrow after induction was associated with significantly improved 2-year PFS outcomes in the combined treatment arms.[53] Final analysis from this trial (455 evaluable patients) confirmed that R-CHOP/R-DHAP induction was associated with higher CR rate (36% vs. 25%) and CR/CRu rate (54% vs. 40%) compared with R-CHOP.[54] After HDT/ASCR, the CR rates were similar between treatment arms (61% vs. 63%), although R-CHOP/R-DHAP was associated with longer remission duration (84 months vs. 49 months; *P*=.0001). After a median

follow up of 51 months, median TTF was significantly longer in the R-CHOP/R-DHAP arm compared with the R-CHOP arm (88 months vs. 46 months; *P*=.038).[54] Moreover, median OS was longer in the R-CHOP/R-DHAP arm (not reached vs. 82 months; *P*=.045). The investigators concluded that an induction regimen containing high-dose cytarabine in addition to R-CHOP resulted in improved outcomes, and suggested that these regimens followed by HDT/ASCR may define a new standard for the treatment of younger patients (<65 years of age) with MCL.[54]

In a phase II multicenter trial of the French cooperative group GELA, induction with 3 cycles each of R-CHOP and R-DHAP resulted in an ORR of 95% with CR in 57% of patients (age ≤65 years) with previously untreated MCL (n=60).[55] Patients went on to receive HDT/ASCR on this study. After a median follow up of 67 months, the median EFS was 83 months and median OS has not been reached; the 5-year OS was 75%.[55]

Post-induction Maintenance Therapy
Maintenance therapy with rituximab may provide extended disease control for patients who are not physically fit or not eligible to undergo aggressive first-line treatment regimens and HDT/ASCR.[57-59]

In a small phase II pilot study in previously untreated patients (n=22), a less intensive, modified R-hyper-CVAD regimen (without methotrexate or cytarabine, and with modifications to dose schedule of vincristine and steroids) followed by rituximab maintenance for 5 years resulted in a median PFS of 37 months with median OS not reached; the use of rituximab maintenance appeared to prolong PFS with acceptable toxicity.[57]

In a subsequent study that incorporated the proteasome inhibitor bortezomib into the modified R-hyper-CVAD (VcR-CVAD regimen) followed by rituximab maintenance in patients with previously untreated MCL (n=30), the CR/CRu rate was 77%.[58] After a median follow up of 42 months, median PFS and OS had not been reached. The 3-year PFS rate was 63% and OS rate was 86%. This VcR-CVAD regimen with maintenance rituximab was further evaluated in a larger phase II ECOG trial (E1405) in patients with previously untreated MCL (n=75).[60] The ORR in this trial was 95% with CR in 68% of patients. Following induction therapy, patients proceeded with maintenance rituximab (n=44) or consolidation with stem cell transplantation (SCT) off protocol (n=22). After a median follow up of 4.5 years, the 3-year PFS and OS rates were 72% and 88% respectively. No differences in PFS or OS were observed between patients who went on to receive rituximab maintenance or SCT.[60]

The European MCL Network recently conducted a phase III randomized trial in older patients (age >60 years not eligible for HDT/ASCR) with previously untreated MCL (n=560; 485 patients evaluable for response) to evaluate induction with R-FC (rituximab, fludarabine and cyclophosphamide) versus R-CHOP, with a second randomization to maintenance with rituximab every 2 months (until relapse; thus, there was no set duration of maintenance rituximab) versus interferon-alfa (given until progression in both arms).[59] Response after induction therapy with R-CHOP and R-FC was similar (CR rate: 34% vs. 40%; CR/CRu rate: 49% vs.53%; ORR: 86% vs. 78%, respectively), but more patients progressed during R-FC than with R-CHOP (14% vs. 5%). Median duration of response was similar between R-FC and R-CHOP arms (37 months vs. 36 months). OS (from start of induction) was significantly longer with R-CHOP compared with R-FC (Median OS: 67 months vs. 40 months; 4-year OS: 62% vs. 47%; *P*=0.005).[59] Grade 3-4

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hematologic toxicities occurred more frequently with R-FC induction. Among the patients who responded to induction and underwent second randomization (n=316), median remission duration was significantly improved with rituximab maintenance compared with interferon alfa (75 months vs. 27 months; *P* <.001). After a median follow up of 42 months, OS outcomes were not significantly different between the two maintenance arms (4-year OS: 79% with rituximab vs. 67% with interferon alfa).[59] However, in the subgroup of patients treated with R-CHOP induction (n=184), median OS (from end of induction) was significantly longer with rituximab maintenance compared with interferon alfa (not reached vs. 64 months; 4-year OS: 87% vs. 63%; *P*=0.005). Moreover, grade 3-4 hematologic toxicities occurred more frequently with interferon alfa. Rituximab was associated with more frequent grade 1-2 infections.[59] This study suggests that for patients who are not candidates for HDT/ASCR as part of first-line therapy, R-CHOP induction followed by rituximab maintenance may offer the best chance to prolong remission duration. Given the positive outcomes reported in this study (with median duration of response exceeding 6 years with rituximab maintenance and a 4-year OS rate of 87% in patients treated with R-CHOP and rituximab maintenance), it is unknown whether first-line consolidation with HDT/ASCR provides an advantage over rituximab maintenance in patients of any age. At the present time, no data are available from randomized studies that would allow direct comparison of outcomes with these two different consolidation approaches.

Relapsed or Refractory Disease

Second-line Therapy
The treatment of patients with relapsed/refractory MCL remains a major challenge, as CR rates are generally low (<30%) and response durations are limited with available regimens.[61]

Bortezomib is a proteasome inhibitor with activity in patients with relapsed or refractory MCL,[62-64] and is currently approved for the treatment of patients with MCL that has relapsed after at least one prior therapy. FDA approval of this agent was based on data from the pivotal phase II PINNACLE trial of single-agent bortezomib in patients with relapsed/refractory MCL (n=155; 141 evaluable patients).[62] In this trial, bortezomib induced an ORR of 33% (CR in 8%), with a median duration of response of 9 months.[62] Median time to progression (in all patients) was 6 months. Longer follow-up data also confirmed these initial findings; after a median follow-up time of 26 months, the median OS in all patients was 23.5 months and was 35 months in responding patients.[65] Small studies have reported promising activity of bortezomib combined with rituximab in heavily pretreated patients with relapsed/refractory MCL.[66,67] In addition, bortezomib in combination with R-hyper-CVAD, with (as discussed above) or without rituximab maintenance, is under investigation in previously untreated patients with MCL.[58,68]

Cladribine has shown activity as a single agent in patients with relapsed MCL.[39,40] In the trial conducted by the North Central Cancer Treatment group, the ORR and median PFS for patients with recurrent MCL (n=25) were 46% (21% CR) and 5 months, respectively.[39]

Fludarabine-based combination regimens, with or without rituximab, have also shown activity in patients with relapsed or refractory MCL.[69-71] Results from a small pilot trial in patients with newly diagnosed and relapsed MCL (20 evaluable patients) showed that the combination of fludarabine, mitoxantrone and rituximab (FMR) induced a CR rate of 90%, with a median duration of CR of 17 months.[70] In patients with MCL (n=66) treated as part of a prospective randomized phase III study of the GLSG, the addition of rituximab to the combination of fludarabine, cyclophosphamide and mitoxantrone (FCM) [R-FCM regimen],

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produced higher ORR (58% vs. 46%) and CR rates (29% vs. 0%) compared with FCM alone.[71,72] This trial included a second randomization to rituximab maintenance versus observation in patients who responded to therapy. In the subgroup of patients with MCL who received R-FCM induction (n=47), rituximab maintenance resulted in a higher proportion of patients in remission beyond 2 years compared with observation only (45% vs. 9%; *P*=0.049); the median duration of remission was similar between maintenance and observation arms (14 months vs. 12 months).[72]

Fludarabine combined with rituximab (FR) was evaluated as part of a phase III randomized trial from StiL that compared FR versus BR in patients with relapsed/refractory follicular or indolent lymphoma or MCL (208 evaluable patients; MCL histology in about 20%).[73] Following a protocol amendment, maintenance therapy with rituximab was also added in both treatment arms (n=40 only). The FR regimen resulted in an ORR and CR rate of 52.5% and 16%, respectively, which was significantly inferior to response rates with BR (ORR 83.5%; CR rate 38.5%). The median PFS with FR was 11 months, which was also significantly shorter compared with a median of 30 months observed with the BR regimen (*P* <.0001).[73] However, no difference in median OS was observed between treatment arms after a median observation time of 33 months.

Bendamustine, as a single agent or in combination with rituximab (BR), has shown promising results with acceptable toxicity in patients with heavily pretreated patients with relapsed or refractory indolent or mantle cell histologies as well as aggressive lymphomas.[73,74] In a phase II multicenter study, BR resulted in an ORR of 92% (41% CR) in patients with relapsed or refractory indolent lymphomas and MCL (n=67).[74] The median duration of response and PFS was 21 months and 23 months, respectively. Outcomes were similar for patients with indolent or mantle

cell histologies. For the subgroup of patients with MCL histology (n=12), the ORR was 92% (42% CR; 17% CRu) and the median duration of response was 19 months.[74] As discussed above, the phase III randomized trial from StiL showed superiority of the BR regimen compared with FR in patients with relapsed/refractory follicular or indolent lymphoma or MCL (208 evaluable patients; MCL histology in about 20%), with an ORR of 83.5% (38.5% CR) and median PFS of 30 months.[73] In a small multicenter phase II study that evaluated the combination of bendamustine and rituximab with bortezomib in patients with relapsed/refractory indolent lymphomas or MCL (29 evaluable patients; MCL histology, n=7), the ORR was 83% (52% CR) and the 2-year PFS rate was 47%.[75] The ORR among the small subgroup of patients with MCL was 71%. Based on these results, this combination regimen is currently being evaluated in randomized trials conducted by the US cooperative groups.

Lenalidomide is an immunomodulating agent that has been evaluated as a single agent in patients with relapsed or refractory aggressive NHL in two phase II studies (NHL-002 and NHL-003).[76-78] In the subset analysis of patients with MCL (n=15) in the NHL-002 study, the ORR was 53% (20% CR).[77] The median duration of response and PFS were 14 months and 6 months, respectively. The subset analysis of patients with MCL (n=54) enrolled in the larger confirmatory study (NHL-003) also showed similar results with an ORR of 43% (17% CR).[78] An updated analysis from the NHL-003 study showed that in the relapsed/refractory MCL subgroup (n=57), the ORR with single-agent lenalidomide was 35% (12% CR/CRu) by independent central review at a median follow up of 12 months.[79] The ORR by investigator review was 44% (21% CR/CRu). By central review, the median duration of response was 16 months and the median PFS was approximately 9 months.[79] Additional phase II studies are specifically evaluating the role

of single-agent lenalidomide in patients with relapsed/refractory MCL. In a phase II study in patients with relapsed/refractory MCL (n=26), lenalidomide (including low-dose lenalidomide maintenance in responding patients) resulted in an ORR of 31% with a median response duration of 22 months.[80] The median PFS was only 4 months. However, among the patients who received maintenance lenalidomide (n=11), the median PFS was 15 months.[80]. In a larger multicenter phase II study (MCL-001) in patients who relapsed after or were refractory to bortezomib (n=134; median 4 prior therapies), lenalidomide as single agent resulted in an ORR of 28% (7.5% CR/CRu) by independent central review.[81] All patients were previously treated with rituximab-containing regimens, and all had relapsed or were refractory to bortezomib. The median duration of response was 16.6 months. The median PFS and OS were was 4 months and 19 months respectively. In the larger studies, the most common grade 3 or 4 toxicities with lenalidomide were myelosuppression (neutropenia in 43%-46% and thrombocytopenia in 28%-30%).[79,81] Lenalidomide combined with rituximab is also under clinical evaluation. In a phase I/II study of a combination regimen with lenalidomide and rituximab in patients with relapsed/refractory MCL (36 evaluable patients), the ORR was 53% (31% CR).[82] The median duration of response was 18 months, and the median PFS (for all patients in the phase II portion) was 14 months. In an updated analysis of this study (n=52), the ORR was 57% (36% CR) among patients treated in the phase II portion (n=44); median duration of response was 19 months.[83] The median PFS was 11 months and median OS was 24 months. The most common grade 3 or 4 toxicities included neutropenia (66%) and thrombocytopenia (23%).[83]

Ibrutinib is a small-molecule inhibitor of Bruton's tyrosine kinase (BTK) involved in the B-cell signalling pathway and has shown promising activity in patients with B-cell malignancies.[84] In a phase I dose-escalation study in patients with relapsed and/or refractory B-cell malignancies (n=56; follicular lymphoma, 29%; CLL/SLL, 29%; MCL, 16%), ibrutinib given in a continuous or intermittent dosing schedule (until progression) resulted in an ORR of 60% (CR in 16%) among evaluable patients (n=50).[84] The median PFS was approximately 14 months. Among the subgroup of patients with MCL (n=9), response was observed in 7 patients, including a CR in 3 patients. Treatment with ibrutinib was well tolerated even with prolonged dosing (> 6 months), with no dose-limiting toxicities and no significant myelosuppression; grade 3 or 4 adverse events were uncommon.[84] The fixed dose of 560 mg daily given continuously was well tolerated and resulted in full occupancy of the BTK target; thus, the recommended phase II dose was established as 560 mg daily. The results of a multicenter phase II study evaluating ibrutinib (560 mg continuous daily dosing until progression) in patients with relapsed or refractory MCL (n=115; median 3 prior therapies, range 1–5), including in patients previously treated with bortezomib have been published.[85] The large majority of patients had received prior rituximab-containing regimens (89%) and 45% were refractory to last therapy before study enrollment. Most patients had advanced disease (72%) and 49% had high-risk disease based on MIPI scores.[85] Among 111 evaluable patients, the estimated median follow up was 15 months at the time of analysis. The ORR was 68% with a CR in 21% of patients. The median duration of response was 17.5 months. Among the subgroup of patients who were previously treated with bortezomib (n=48), the ORR was 67% with a CR in 23%. The response rates appeared to increase with longer duration of therapy. The estimated median PFS for all treated patients was approximately 14 months. Median OS has not yet been reached; the estimated OS rate at 18 months was 58%. The most common grade 3 or greater adverse events included neutropenia (16%), thrombocytopenia (11%), anemia (10%), pneumonia (6%), diarrhea

(6%), fatigue (5%) and dyspnea (5%).[85] This study showed durable responses with single-agent ibrutinib with a favorable toxicity profile. The use of ibrutinib has been known to result in an initial transient lymphocytosis which resolves by a median of 8 weeks after initiation of ibrutinib.[86] Ibrutinib treatment has also been associated with grade ≥ 3 bleeding events in 5% of patients.[86] The benefit and risk of ibrutinib should be considered in patients requiring anti-platelet or anticoagulant therapies. See *"Special Considerations for the use of BCR Inhibitors"* in the guidelines for monitoring and management of adverse reactions associated with ibrutinib.

Based on these data, ibrutinib (560 mg orally, once daily) was recently approved by the FDA for the treatment of patients with MCL who received at least one prior therapy.

Second-Line Consolidation Therapy
In patients with relapsed/refractory indolent NHL, allogeneic stem cell transplant (SCT) has resulted in decreased rates of disease recurrence compared with HDT/ASCR, but at the cost of a higher treatment-related mortality (TRM) rate.[87,88]

In an effort to reduce the TRM associated with allogeneic SCT, the use of reduced-intensity conditioning (RIC) regimens has been explored. In a study that evaluated allogeneic SCT using conventional myeloablative conditioning or RIC in patients with relapsed/refractory NHL (n=25), RIC (fludarabine-based regimens) was associated with a decreased TRM rate (17% vs. 54%) and increased event-free survival (50% vs. 23%) and OS (67% vs. 23%) rates at 1 year compared with myeloablative regimens.[89] A multicenter retrospective study of RIC allogeneic SCT in patients with relapsed/refractory low-grade NHL (n=73) also reported promising long-term outcomes with RIC (primarily using fludarabine-based regimens); in this study, the 3-year EFS and OS

rates were 51% and 56%, respectively.[90] Although the 3-year relapse rate appeared low at 10%, the TRM rate was high, with a 3-year cumulative incidence of 40%.[90] Allogeneic SCT using RIC has been evaluated as a consolidation strategy for patients in remission following treatment for relapsed/refractory MCL.[47,91,92] In patients with relapsed MCL treated with RIC allogeneic SCT (n=18), the 3-year PFS rate and estimated 3-year OS rate was 82% and 85.5%, respectively; the majority of patients in this study (89%) had chemosensitive disease.[91] In another study, RIC allogeneic SCT was evaluated in patients with relapsed/refractory MCL (n=33); 42% of these patients had failed prior HDT/ASCR.[92] The 2-year disease-free survival and OS rates were 60% and 65%, respectively. The 2-year relapse rate was 9%; moreover, with a median follow up of nearly 25 months, none of the patients transplanted in a CR (n=13) experienced disease relapse.[92] The 2-year TRM rate in this study was 24%. In an analysis of patients with MCL treated with SCT at the MD Anderson Cancer Center, the subgroup of patients with relapsed/refractory disease treated with RIC allogeneic SCT (n=35) had favorable long-term outcomes.[47] Most of these patients (62%) were transplanted in remission (31% in second remission). The analysis reported a median PFS of 60 months, and 6-year PFS and OS rates of 46% and 53%, respectively. The TRM rates at 3 months and 1 year were 0% and 9%, respectively.[47]

NCCN Recommendations for Stage I-II

Recommendations for First-line Therapy and Follow-up
Outside of a clinical trial, the NCCN Guidelines panel recommends RT (30-36 Gy) alone or combination chemoimmunotherapy with or without RT. These recommendations are based on treatment principles in the absence of more definitive clinical data.

For patients with a CR, clinical follow up should be conducted every 3-6 months for the first 5 years, and then on a yearly basis or as clinically

indicated. If the patient received initial treatment with chemoimmunotherapy with or without RT, and relapses after an initial CR (or the initial response is a PR or disease progression on first-line therapy), the patient should be treated with second-line therapy regimens recommended for stage II (bulky) or stage III-IV disease (see sections below). If the patient received initial treatment with RT alone and relapses after achieving a CR (or the initial response is a PR or disease progression with RT alone), then the patient can be treated with first-line induction therapy (comprising chemoimmunotherapy regimens) recommended for stage II (bulky) and stage III-IV disease.

NCCN Recommendations for Stage II (bulky) and Stage III-IV

Recommendations for First-line Therapy and Follow-up

In the absence of standard management for patients with advanced disease, patients should be referred for participation in prospective clinical trials. Similar to the management of patients with indolent lymphomas, patients with MCL often require highly individualized courses of care. The majority of patients with MCL will have advanced stage disease and require systemic therapy. However, in highly selected patients with asymptomatic disease, close observation with deferred therapy is a reasonable option, especially for those with good performance status and lower risk scores on standard IPI.[93] The standard treatment regimen for MCL is not yet established. There are no prospective randomized studies comparing the various aggressive induction regimens for MCL, although some randomized data exist for less intensive first-line treatment options (as previously discussed). Given the role of rituximab in the treatment of CD20-positive NHL, it is reasonable to consider rituximab-containing regimens for management of advanced MCL. Based on the available data, the NCCN Guideline panel has included the following regimens for initial induction therapy:

All regimens listed below (except for hyper-CVAD + rituximab) included first-line consolidation with HDT/ASCR in published reports.

- Hyper-CVAD + rituximab[32-34]
- Dose-intensified CHOP [maxi-CHOP] alternating with rituximab + high-dose cytarabine[51]
- Rituximab and methotrexate with augmented CHOP[52]
- Sequential R-CHOP and R-ICE[16]
- Alternating R-CHOP and R-DHAP[53]
- *Less aggressive therapy:*
- Bendamustine + rituximab[37]
- CHOP + rituximab [R-CHOP][29,36]
- Cladribine + rituximab[39,41]
- Modified Hyper-CVAD with rituximab maintenance in patients older than 65 years[57]

For patients with a CR to first-line therapy, participation in a clinical trial or HDT/ASCR is recommended for eligible patients (see section below). For patients with a CR, clinical follow up should be conducted every 3-6 months for the first 5 years, and then on a yearly basis or as clinically indicated. For patients with only a PR to first-line therapy, additional therapy (see second-line therapy regimens below) may be considered in an effort to improve the quality of a response. If the patient achieves a CR (or improved PR) with additional therapy, consolidation with HDT/ASCR may be considered for eligible patients, as discussed above. For patients who relapse after achieving a remission to first-line therapy, or for patients who experience disease progression during initial therapy, participation in clinical trials is preferred. In the absence of suitable clinical trials, second-line treatment options can be considered.

Recommendations for First-line Consolidation Therapy

The panel recommends consolidation with HDT/ASCR for eligible patients in remission following first-line therapy, although no studies have compared maintenance rituximab with HDT/ASCR for patients in first CR. In general, patients will receive an aggressive induction regimen prior to consolidation; however, less aggressive induction therapy followed by consolidation with HDT/ASCR or maintenance rituximab may also result in good long-term outcome.

For patients who are not candidates for HDT/ASCR, and who are in remission after first-line therapy with R-CHOP, maintenance treatment with rituximab (every 8 weeks until disease progression) is recommended (category 1)[59]

Recommendations for Second-line Therapy

The optimal approach to relapsed or refractory disease remains to be defined. Patients with relapsed disease following CR to induction therapy or those who obtain only a PR to induction therapy or those with progressive disease are appropriate candidates for clinical trials involving HDT/ASCR or allogeneic HSCT, immunotherapy with nonmyeloablative stem cell rescue or treatment with new agents. Based on the recent FDA approval, the panel has included ibrutinib as an option for second-line therapy for patients with relapsed or refractory disease.[85] Alternatively, in the absence of an appropriate clinical trial, these patients can be treated with second-line chemotherapy regimens (with or without rituximab) recommended for patients with DLBCL or any of the following regimens:

- Bendamustine ± rituximab[73]
- Bortezomib ± rituximab[65,66]
- Cladribine ± rituximab[39,40]

- FC (fludarabine, cyclophosphamide) ± rituximab[69]
- FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab)[71]
- FMR (fludarabine, mitoxantrone, rituximab)[70]
- Lenalidomide ± rituximab[81,94]
- PCR (pentostatin, cyclophosphamide, rituximab)
- PEPC (prednisone, etoposide, procarbazine, cyclophosphamide) ± rituximab[95]

Allogeneic transplantation (with myeloablative or reduced intensity conditioning) is an appropriate option for patients with relapsed or refractory disease that is in remission following second-line therapy.[47,91,92]

References

1. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 1997;89:3909-3918. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9166827.

2. Fisher RI, Dahlberg S, Nathwani BN, et al. A clinical analysis of two indolent lymphoma entities: mantle cell lymphoma and marginal zone lymphoma (including the mucosa-associated lymphoid tissue and monocytoid B-cell subcategories): a Southwest Oncology Group study. Blood 1995;85:1075-1082. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7849295.

3. Yatabe Y, Suzuki R, Tobinai K, et al. Significance of cyclin D1 overexpression for the diagnosis of mantle cell lymphoma: a clinicopathologic comparison of cyclin D1-positive MCL and cyclin D1-negative MCL-like B-cell lymphoma. Blood 2000;95:2253-2261. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10733493.

4. Hartmann EM, Campo E, Wright G, et al. Pathway discovery in mantle cell lymphoma by integrated analysis of high-resolution gene expression and copy number profiling. Blood 2010;116:953-961. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20421449.

5. Iqbal J, Shen Y, Liu Y, et al. Genome-wide miRNA profiling of mantle cell lymphoma reveals a distinct subgroup with poor prognosis. Blood 2012;119:4939-4948. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22490335.

6. Fu K, Weisenburger DD, Greiner TC, et al. Cyclin D1-negative mantle cell lymphoma: a clinicopathologic study based on gene expression profiling. Blood 2005;106:4315-4321. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16123218.

7. Wlodarska I, Dierickx D, Vanhentenrijk V, et al. Translocations targeting CCND2, CCND3, and MYCN do occur in t(11;14)-negative mantle cell lymphomas. Blood 2008;111:5683-5690. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18391076.

8. Salaverria I, Royo C, Carvajal-Cuenca A, et al. CCND2 rearrangements are the most frequent genetic events in cyclin D1(-) mantle cell lymphoma. Blood 2013;121:1394-1402. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23255553.

9. Chen YH, Gao J, Fan G, Peterson LC. Nuclear expression of sox11 is highly associated with mantle cell lymphoma but is independent of t(11;14)(q13;q32) in non-mantle cell B-cell neoplasms. Mod Pathol 2010;23:105-112. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19801969.

10. Mozos A, Royo C, Hartmann E, et al. SOX11 expression is highly specific for mantle cell lymphoma and identifies the cyclin D1-negative subtype. Haematologica 2009;94:1555-1562. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19880778.

11. Zeng W, Fu K, Quintanilla-Fend L, et al. Cyclin D1-negative blastoid mantle cell lymphoma identified by SOX11 expression. Am J Surg Pathol 2012;36:214-219. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22251940.

12. Avet-Loiseau H, Garand R, Gaillard F, et al. Detection of t(11;14) using interphase molecular cytogenetics in mantle cell lymphoma and atypical chronic lymphocytic leukemia. Genes Chromosomes Cancer 1998;23:175-182. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9739021.

13. Determann O, Hoster E, Ott G, et al. Ki-67 predicts outcome in advanced-stage mantle cell lymphoma patients treated with anti-CD20 immunochemotherapy: results from randomized trials of the European MCL Network and the German Low Grade Lymphoma Study Group. Blood 2008;111:2385-2387. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18077791.

14. Garcia M, Romaguera JE, Inamdar KV, et al. Proliferation predicts failure-free survival in mantle cell lymphoma patients treated with rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with rituximab plus high-

dose methotrexate and cytarabine. Cancer 2009;115:1041-1048. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19170236.

15. Hsi ED, Jung S, Lai R, et al. Ki67 and PIM1 expression predict outcome in mantle cell lymphoma treated with high dose therapy, stem cell transplantation and rituximab: a Cancer and Leukemia Group B 59909 correlative science study. Leuk Lymphoma 2008;49:2081-2090. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19021050.

16. Schaffel R, Hedvat CV, Teruya-Feldstein J, et al. Prognostic impact of proliferative index determined by quantitative image analysis and the International Prognostic Index in patients with mantle cell lymphoma. Ann Oncol 2010;21:133-139. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20019090.

17. Tiemann M, Schrader C, Klapper W, et al. Histopathology, cell proliferation indices and clinical outcome in 304 patients with mantle cell lymphoma (MCL): a clinicopathological study from the European MCL Network. Br J Haematol 2005;131:29-38. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16173960.

18. Koletsa T, Markou K, Ouzounidou S, et al. In situ mantle cell lymphoma in the nasopharynx. Head Neck 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23280758.

19. Richard P, Vassallo J, Valmary S, et al. "In situ-like" mantle cell lymphoma: a report of two cases. J Clin Pathol 2006;59:995-996. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16935977.

20. Carvajal-Cuenca A, Sua LF, Silva NM, et al. In situ mantle cell lymphoma: clinical implications of an incidental finding with indolent clinical behavior. Haematologica 2012;97:270-278. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22058203.

21. Swerdlow SH, Campo E, Seto M, Muller-Hermelink HK. Mantle cell lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:229-232.

22. Edlefsen KL, Greisman HA, Yi HS, et al. Early lymph node involvement by mantle cell lymphoma limited to the germinal center: report of a case with a novel "follicular in situ" growth pattern. Am J Clin Pathol 2011;136:276-281. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21757601.

23. Adam P, Schiefer AI, Prill S, et al. Incidence of preclinical manifestations of mantle cell lymphoma and mantle cell lymphoma in situ in reactive lymphoid tissues. Mod Pathol 2012;25:1629-1636. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22790016.

24. Carbone A, Santoro A. How I treat: diagnosing and managing "in situ" lymphoma. Blood 2011;117:3954-3960. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21224472.

25. Romaguera JE, Medeiros LJ, Hagemeister FB, et al. Frequency of gastrointestinal involvement and its clinical significance in mantle cell lymphoma. Cancer 2003;97:586-591. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12548600.

26. Salar A, Juanpere N, Bellosillo B, et al. Gastrointestinal involvement in mantle cell lymphoma: a prospective clinic, endoscopic, and pathologic study. Am J Surg Pathol 2006;30:1274-1280. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17001159.

27. Teodorovic I, Pittaluga S, Kluin-Nelemans JC, et al. Efficacy of four different regimens in 64 mantle-cell lymphoma cases: clinicopathologic comparison with 498 other non-Hodgkin's lymphoma subtypes. European Organization for the Research and Treatment of Cancer Lymphoma Cooperative Group. J Clin Oncol 1995;13:2819-2826. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7595744.

28. Leitch HA, Gascoyne RD, Chhanabhai M, et al. Limited-stage mantle-cell lymphoma. Ann Oncol 2003;14:1555-1561. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14504058.

29. Martin P, Chadburn A, Christos P, et al. Intensive treatment strategies may not provide superior outcomes in mantle cell lymphoma:

overall survival exceeding 7 years with standard therapies. Ann Oncol 2008;19:1327-1330. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18349031.

30. Lacasce AS, Vandergrift JL, Rodriguez MA, et al. Comparative outcome of initial therapy for younger patients with mantle cell lymphoma: an analysis from the NCCN NHL Database. Blood 2012;119:2093-2099. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22234679.

31. Romaguera JE, Fayad L, Rodriguez MA, et al. High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. J Clin Oncol 2005;23:7013-7023. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16145068.

32. Romaguera JE, Fayad LE, Feng L, et al. Ten-year follow-up after intense chemoimmunotherapy with Rituximab-HyperCVAD alternating with Rituximab-high dose methotrexate/cytarabine (R-MA) and without stem cell transplantation in patients with untreated aggressive mantle cell lymphoma. Br J Haematol 2010;150:200-208. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20528872.

33. Merli F, Luminari S, Ilariucci F, et al. Rituximab plus HyperCVAD alternating with high dose cytarabine and methotrexate for the initial treatment of patients with mantle cell lymphoma, a multicentre trial from Gruppo Italiano Studio Linfomi. Br J Haematol 2012;156:346-353. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22145911.

34. Bernstein SH, Epner E, Unger JM, et al. A phase II multicenter trial of hyperCVAD MTX/Ara-C and rituximab in patients with previously untreated mantle cell lymphoma; SWOG 0213. Ann Oncol 2013;24:1587-1593. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23504948.

35. Howard OM, Gribben JG, Neuberg DS, et al. Rituximab and CHOP induction therapy for newly diagnosed mantle-cell lymphoma: molecular

complete responses are not predictive of progression-free survival. J Clin Oncol 2002;20:1288-1294. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11870171.

36. Lenz G, Dreyling M, Hoster E, et al. Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). J Clin Oncol 2005;23:1984-1992. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15668467.

37. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet 2013;381:1203-1210. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23433739.

38. Visco C, Finotto S, Zambello R, et al. Combination of rituximab, bendamustine, and cytarabine for patients with mantle-cell non-Hodgkin lymphoma ineligible for intensive regimens or autologous transplantation. J Clin Oncol 2013;31:1442-1449. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23401442.

39. Inwards DJ, Fishkin PA, Hillman DW, et al. Long-term results of the treatment of patients with mantle cell lymphoma with cladribine (2-CDA) alone (95-80-53) or 2-CDA and rituximab (N0189) in the North Central Cancer Treatment Group. Cancer 2008;113:108-116. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18470909.

40. Rummel MJ, Chow KU, Jager E, et al. Treatment of mantle-cell lymphomas with intermittent two-hour infusion of cladribine as first-line therapy or in first relapse. Ann Oncol 1999;10:115-117. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10076731.

41. Spurgeon SE, Pindyck T, Okada C, et al. Cladribine plus rituximab is an effective therapy for newly diagnosed mantle cell lymphoma. Leuk

Lymphoma 2011;52:1488-1494. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21623691.

42. Khouri IF, Romaguera J, Kantarjian H, et al. Hyper-CVAD and high-dose methotrexate/cytarabine followed by stem-cell transplantation: an active regimen for aggressive mantle-cell lymphoma. J Clin Oncol 1998;16:3803-3809. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9850025.

43. Khouri IF, Saliba RM, Okoroji GJ, et al. Long-term follow-up of autologous stem cell transplantation in patients with diffuse mantle cell lymphoma in first disease remission: the prognostic value of beta2-microglobulin and the tumor score. Cancer 2003;98:2630-2635. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14669282.

44. Lefrere F, Delmer A, Suzan F, et al. Sequential chemotherapy by CHOP and DHAP regimens followed by high-dose therapy with stem cell transplantation induces a high rate of complete response and improves event-free survival in mantle cell lymphoma: a prospective study. Leukemia 2002;16:587-593. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11960337.

45. Dreyling M, Lenz G, Hoster E, et al. Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: results of a prospective randomized trial of the European MCL Network. Blood 2005;105:2677-2684. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15591112.

46. Ritchie DS, Seymour JF, Grigg AP, et al. The hyper-CVAD-rituximab chemotherapy programme followed by high-dose busulfan, melphalan and autologous stem cell transplantation produces excellent event-free survival in patients with previously untreated mantle cell lymphoma. Ann Hematol 2007;86:101-105. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17089127.

47. Tam CS, Bassett R, Ledesma C, et al. Mature results of the M. D. Anderson Cancer Center risk-adapted transplantation strategy in mantle

cell lymphoma. Blood 2009;113:4144-4152. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19168784.

48. van 't Veer MB, de Jong D, MacKenzie M, et al. High-dose Ara-C and beam with autograft rescue in R-CHOP responsive mantle cell lymphoma patients. Br J Haematol 2009;144:524-530. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19036081.

49. Till BG, Gooley TA, Crawford N, et al. Effect of remission status and induction chemotherapy regimen on outcome of autologous stem cell transplantation for mantle cell lymphoma. Leuk Lymphoma 2008;49:1062-1073. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18452065.

50. Vandenberghe E, Ruiz de Elvira C, Loberiza FR, et al. Outcome of autologous transplantation for mantle cell lymphoma: a study by the European Blood and Bone Marrow Transplant and Autologous Blood and Marrow Transplant Registries. Br J Haematol 2003;120:793-800. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12614212.

51. Geisler CH, Kolstad A, Laurell A, et al. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. Blood 2008;112:2687-2693. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18625886.

52. Damon LE, Johnson JL, Niedzwiecki D, et al. Immunochemotherapy and autologous stem-cell transplantation for untreated patients with mantle-cell lymphoma: CALGB 59909. J Clin Oncol 2009;27:6101-6108. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19917845.

53. Pott C, Hoster E, Beldjord K, et al. R-CHOP/R-DHAP compared to R-CHOP induction followed by high dose therapy with autologous stem cell transplantation induces higher rates of molecular remission in MCL: results of the MCL younger intergroup trial of the European MCL Network [abstract]. Blood 2010;116:Abstract 965. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/965.

54. Hermine O, Hoster E, Walewski J, et al. Alternating Courses of 3x CHOP and 3x DHAP Plus Rituximab Followed by a High Dose ARA-C Containing Myeloablative Regimen and Autologous Stem Cell Transplantation (ASCT) Increases Overall Survival When Compared to 6 Courses of CHOP Plus Rituximab Followed by Myeloablative Radiochemotherapy and ASCT in Mantle Cell Lymphoma: Final Analysis of the MCL Younger Trial of the European Mantle Cell Lymphoma Network (MCL net) [abstract]. Blood 2012;120:Abstract 151. Available at:
http://abstracts.hematologylibrary.org/cgi/content/abstract/120/21/151.

55. Delarue R, Haioun C, Ribrag V, et al. CHOP and DHAP plus rituximab followed by autologous stem cell transplantation in mantle cell lymphoma: a phase 2 study from the Groupe d'Etude des Lymphomes de l'Adulte. Blood 2013;121:48-53. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/22718839.

56. Geisler CH, Kolstad A, Laurell A, et al. Nordic MCL2 trial update: six-year follow-up after intensive immunochemotherapy for untreated mantle cell lymphoma followed by BEAM or BEAC + autologous stem-cell support: still very long survival but late relapses do occur. Br J Haematol 2012;158:355-362. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/22640180.

57. Kahl BS, Longo WL, Eickhoff JC, et al. Maintenance rituximab following induction chemoimmunotherapy may prolong progression-free survival in mantle cell lymphoma: a pilot study from the Wisconsin Oncology Network. Ann Oncol 2006;17:1418-1423. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/16766582.

58. Chang JE, Peterson C, Choi S, et al. VcR-CVAD induction chemotherapy followed by maintenance rituximab in mantle cell lymphoma: a Wisconsin Oncology Network study. Br J Haematol 2011;155:190-197. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/21848883.

59. Kluin-Nelemans HC, Hoster E, Hermine O, et al. Treatment of older patients with mantle-cell lymphoma. N Engl J Med 2012;367:520-531. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22873532.

60. Chang JE, Li H, Smith MR, et al. Phase II study of VcR-CVAD with maintenance rituximab for untreated mantle cell lymphoma: an Eastern Cooperative Oncology Group Study (E1405). Blood 2014;123:1665-1673. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24458437.

61. Goy A, Kahl B. Mantle cell lymphoma: the promise of new treatment options. Crit Rev Oncol Hematol 2011;80:69-86. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/21168343.

62. Fisher RI, Bernstein SH, Kahl BS, et al. Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. J Clin Oncol 2006;24:4867-4874. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/17001068.

63. Belch A, Kouroukis CT, Crump M, et al. A phase II study of bortezomib in mantle cell lymphoma: the National Cancer Institute of Canada Clinical Trials Group trial IND.150. Ann Oncol 2007;18:116-121. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16971665.

64. O'Connor OA, Moskowitz C, Portlock C, et al. Patients with chemotherapy-refractory mantle cell lymphoma experience high response rates and identical progression-free survivals compared with patients with relapsed disease following treatment with single agent bortezomib: results of a multicentre phase 2 clinical trial. British Journal of Haematology 2009;145:34-39. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/19220284.

65. Goy A, Bernstein SH, Kahl BS, et al. Bortezomib in patients with relapsed or refractory mantle cell lymphoma: updated time-to-event analyses of the multicenter phase 2 PINNACLE study. Ann Oncol 2009;20:520-525. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/19074748.

66. Baiocchi RA, Alinari L, Lustberg ME, et al. Phase 2 trial of rituximab and bortezomib in patients with relapsed or refractory mantle cell and follicular lymphoma. Cancer 2011;117:2442-2451. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21157957.

67. Lamm W, Kaufmann H, Raderer M, et al. Bortezomib combined with rituximab and dexamethasone is an active regimen for patients with relapsed and chemotherapy-refractory mantle cell lymphoma. Haematologica 2011;96:1008-1014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21486866.

68. Romaguera JE, Fayad LE, McLaughlin P, et al. Phase I trial of bortezomib in combination with rituximab-HyperCVAD alternating with rituximab, methotrexate and cytarabine for untreated aggressive mantle cell lymphoma. Br J Haematol 2010;151:47-53. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20735402.

69. Cohen BJ, Moskowitz C, Straus D, et al. Cyclophosphamide/fludarabine (CF) is active in the treatment of mantle cell lymphoma. Leuk Lymphoma 2001;42:1015-1022. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11697618.

70. Levine AM, Tulpule A, Smith L, et al. Results of a pilot trial of fludarabine, mitoxantrone and Rituxan in mantle cell lymphoma [abstract]. Blood 2005;106:Abstract 945. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/106/11/945.

71. Forstpointner R, Dreyling M, Repp R, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2004;104:3064-3071. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15284112.

72. Forstpointner R, Unterhalt M, Dreyling M, et al. Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG). Blood 2006;108:4003-4008. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16946304.

73. Rummel MJ, Kaiser U, Balser C, et al. Bendamustine plus rituximab versus fludarabine plus rituximab in patients with relapsed follicular, indolent and mantle cell lymphomas - final results of the randomized phase III study NHL 2-2003 on behalf of the StiL (Study Group Indolent Lymphomas, Germany) [abstract]. Blood 2010;116:Abstract 856. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/856.

74. Robinson KS, Williams ME, van der Jagt RH, et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma. J Clin Oncol 2008;26:4473-4479. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18626004.

75. Friedberg JW, Vose JM, Kelly JL, et al. The combination of bendamustine, bortezomib, and rituximab for patients with relapsed/refractory indolent and mantle cell non-Hodgkin lymphoma. Blood 2011;117:2807-2812. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21239695.

76. Wiernik PH, Lossos IS, Tuscano JM, et al. Lenalidomide monotherapy in relapsed or refractory aggressive non-Hodgkin's lymphoma. J Clin Oncol 2008;26:4952-4957. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18606983.

77. Habermann TM, Lossos IS, Justice G, et al. Lenalidomide oral monotherapy produces a high response rate in patients with relapsed or refractory mantle cell lymphoma. Br J Haematol 2009;145:344-349. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19245430.

78. Reeder CB, Witzig TE, Zinzani PL, et al. Efficacy and safety of lenalidomide oral monotherapy in patients with relapsed or refractory mantle-cell lymphoma: Results from an international study (NHL-003) [abstract]. J Clin Oncol 2009;27:Abstract 8569. Available at: http://meeting.ascopubs.org/cgi/content/abstract/27/15S/8569.

79. Zinzani PL, Vose JM, Czuczman MS, et al. Phase II Multicenter Study of the Safety and Efficacy of Single-Agent Lenalidomide in Subjects with Relapsed/Refractory Mantle Cell Lymphoma: Long-Term Follow-up Analysis of the NHL-003 Study [abstract]. Blood 2012;120:Abstract 2738. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/120/21/2738.

80. Eve HE, Carey S, Richardson SJ, et al. Single-agent lenalidomide in relapsed/refractory mantle cell lymphoma: results from a UK phase II study suggest activity and possible gender differences. Br J Haematol 2012;159:154-163. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22881386.

81. Goy A, Sinha R, Williams ME, et al. Single-agent lenalidomide in patients with mantle-cell lymphoma who relapsed or progressed after or were refractory to bortezomib: phase II MCL-001 (EMERGE) study. J Clin Oncol 2013;31:3688-3695. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24002500.

82. Wang L, Fayad L, Hagemeister FB, et al. A phase I/IIstudy of lenalidomide in combination with rituximab in relapsed/refractory mantle cell lymphoma [abstract]. Blood 2009;114:Abstract 2719. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/114/22/2719.

83. Wang M, Fayad L, Wagner-Bartak N, et al. Lenalidomide in combination with rituximab for patients with relapsed or refractory mantle-cell lymphoma: a phase 1/2 clinical trial. Lancet Oncol 2012;13:716-723. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22677155.

84. Advani RH, Buggy JJ, Sharman JP, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. J Clin Oncol 2013;31:88-94. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23045577.

85. Wang ML, Rule S, Martin P, et al. Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma. N Engl J Med 2013;369:507-516. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23782157.

86. Full prescribing information for ibrutinib. 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/205552lbl.pdf.

87. Hosing C, Saliba RM, McLaughlin P, et al. Long-term results favor allogeneic over autologous hematopoietic stem cell transplantation in patients with refractory or recurrent indolent non-Hodgkin's lymphoma. Ann Oncol 2003;14:737-744. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12702528.

88. van Besien K, Loberiza FR, Bajorunaite R, et al. Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. Blood 2003;102:3521-3529. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12893748.

89. Bertz H, Illerhaus G, Veelken H, Finke J. Allogeneic hematopoetic stem-cell transplantation for patients with relapsed or refractory lymphomas: comparison of high-dose conventional conditioning versus fludarabine-based reduced-intensity regimens. Ann Oncol 2002;13:135-139. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11863095.

90. Vigouroux S, Michallet M, Porcher R, et al. Long-term outcomes after reduced-intensity conditioning allogeneic stem cell transplantation for low-grade lymphoma: a survey by the French Society of Bone Marrow Graft Transplantation and Cellular Therapy (SFGM-TC). Haematologica 2007;92:627-634. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17488686.

91. Khouri IF, Lee MS, Saliba RM, et al. Nonablative allogeneic stem-cell transplantation for advanced/recurrent mantle-cell lymphoma. J Clin

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Oncol 2003;21:4407-4412. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/14645431.

92. Maris MB, Sandmaier BM, Storer BE, et al. Allogeneic hematopoietic cell transplantation after fludarabine and 2 Gy total body irradiation for relapsed and refractory mantle cell lymphoma. Blood 2004;104:3535-3542. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/15304387.

93. Martin P, Chadburn A, Christos P, et al. Outcome of deferred initial therapy in mantle-cell lymphoma. J Clin Oncol 2009;27:1209-1213. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19188674.

94. Witzig TE, Vose JM, Zinzani PL, et al. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. Ann Oncol 2011;22:1622-1627. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/21228334.

95. Coleman M, Martin P, Ruan J, et al. Prednisone, etoposide, procarbazine, and cyclophosphamide (PEP-C) oral combination chemotherapy regimen for recurring/refractory lymphoma: low-dose metronomic, multidrug therapy. Cancer 2008;112:2228-2232. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18338745.

Diffuse Large B-Cell Lymphoma

Diagnosis

Diffuse large B-cell lymphomas (DLBCL) are the most common lymphoid neoplasms in adults, accounting for approximately 30% of NHLs diagnosed annually.[1] DLBCL NOS, FL (grade 3 only), DLBCL coexistent with a low-grade lymphoma of any kind (e.g., FL of any grade, gastric MALT or non-gastric MALT lymphoma), intravascular large B-cell lymphoma, DLBCL associated with chronic inflammation, ALK-positive DLBCL, EBV-positive DLBCL of the elderly and T-cell/histiocyte rich large B-cell lymphoma are also managed according to the DLBCL guidelines.

Gene expression profiling studies have revealed significant heterogeneity within DLBCL.[2] However, incorporation of this information into treatment algorithms awaits further investigation. Immunohistochemical markers such as CD10, BCL6, and IRF4/MUM1 have been reported to recapitulate the gene expression profiling in classifying DLBCL into 2 different subtypes: germinal center B-cell (GCB) subtype (CD10+, or BCL6+, IRF4/MUM1-) and non-GCB subtype (CD10-, IRF4/MUM1+ or BCL6-, IRF4/MUM1-).[3] However, the validity of this classification has been brought into question. An improved immunohistochemical algorithm has been proposed which includes GCET1, FOXP1, BCL6, IFR4/MUM1, and CD10.[4,5] Although GCB subtype is associated with an improved outcome compared to non-GCB subtype, treatment remains the same for both the subtypes and cell-of-origin should not be used to guide the selection of therapy.

MYC rearrangement has been reported in 9% to 17% of patients with DLBCL, and often correlates with GCB phenotype.[6-8] DLBCL with concurrent *BCL2* and *MYC* rearrangements are known as "double-hit" lymphomas that are characterized by highly aggressive clinical behavior and overlapping pathologic features with Burkitt lymphoma (BL), B lymphoblastic lymphoma/leukemia (B-LBL), and DLBCL.[9] "Double-hit" lymphomas have been observed in 2% to 11% of newly diagnosed patients with DLBCL. Patients with "double-hit" lymphomas have very poor clinical outcomes, even with rituximab-containing chemoimmunotherapy or intensive therapy with stem cell transplantation.[6-8,10] Immunohistochemical staining can also identify DLBCL with dual expression of both MYC and BCL2 proteins ("double-expressing" DLBCL).[11,12] These patients have an inferior prognosis compared to those with DLBCL as a whole, but not to the same magnitude as patients with true "double-hit" lymphomas on the basis of genetic rearrangements. No guidelines are available for the treatment of patients with "double-hit" lymphomas with concurrent *MYC* and *BCL2* rearrangements nor for "double-expressing" lymphomas, as the standard of care for these patients have not been established. Additional data on the management of these high-risk disease subtypes is needed.

Adequate immunophenotyping is required to establish the diagnosis and to determine GCB versus non-GCB origin. The typical immunophenotype is CD20+, CD45+, and CD3-. The recommended immunophenotyping panel includes CD20, CD3, CD5, CD10, CD45, BCL2, BCL6, Ki-67, IRF4/MUM1 and MYC. When available, GCET1 and FOXP1 can provide information necessary for the Choi IHC cell of origin algorithm. Additional markers such as CD138, CD30, cyclin D1, ALK1, EBV and HHV-8 may be useful under certain circumstances to establish the subtype. Molecular genetic analysis for detection of gene rearrangements in *CCND1, BCL6*, or *MYC*, as well as conventional or FISH cytogenetic for detection of the translocations, t(14;18), t(3;v), t(8;14) or t(8;v) may also be useful in some cases.

Workup

The initial workup for newly diagnosed patients with DLBCL should include a thorough physical examination with attention to node-bearing areas, and evaluation of performance status and constitutional symptoms. Laboratory assessments should include standard blood work including CBC with differential and a comprehensive metabolic panel, in addition to measurements of serum lactate dehydrogenase (LDH) and serum beta-2-microglobulin levels. Patients with high tumor burden and elevated LDH should be assessed for spontaneous tumor lysis syndrome, including measurements of uric acid level. HBV testing is recommended due to increased risks of viral reactivation when immunotherapy regimens are being considered for treatment. Adequate trephine biopsy (specimen ≥1.6 cm)[13,14] should be obtained for initial staging evaluation, with or without bone marrow aspiration.

The staging workup is designed to identify all sites of known disease and determine prognosis with known clinical risk factors. Risk factors used to determine International Prognostic Index (IPI) scores include age, stage of disease, LDH level, performance status, and the number of extra-nodal sites of disease.[15] In patients who are 60 years or younger, the prognostic factors include tumor stage, performance status, and serum LDH level. The IPI and age-adjusted IPI can be used to identify specific group of patients who are more or less likely to be cured with standard therapy.[15] Zhou et al recently reported an enhanced IPI (NCCN-IPI) to stratify patients with newly diagnosed DLBCL into 4 different risk groups (low, low-intermediate, high-intermediate, and high) based on their clinical features (age, LDH, sites of involvement, Ann Arbor stage, ECOG performance status).[16] This analysis included 1650 patients identified in NCCN database who were diagnosed with DLBCL from 2000-2010 and treated with rituximab-based therapy. The NCCN-IPI discriminated patients in the low- and high-risk subgroups

better (5-year OS rate 96% vs 33%) than the IPI (5 year OS rate 90% vs 54%). NCCN-IPI was also validated using an independent cohort of 1138 patients from the British Columbia Cancer Agency.

PET or PET-CT scans, have a more clear-cut role in selected cases of DLBCL than in other lymphoid neoplasms. PET scans are particularly informative in the initial staging where upstaging resulting in altered therapy occurs about 9% of the time, and for response evaluation after treatment because they can distinguish residual fibrotic masses from masses containing viable tumor. As PET scans have now been incorporated into the response criteria, availability of a baseline study is necessary for optimal interpretation of the post-treatment study. In some centers, beta-2-microglobulin is considered a major determinant of risk (category 2B). Lumbar puncture is recommended in patients with one or more of the following sites of involvement: paranasal sinus, testicular, epidural, HIV-associated lymphoma, bone marrow (with large cells) or the presence of 2 or more extranodal sites and elevated LDH levels. Diagnostic yield is improved if flow cytometric analysis of CSF is undertaken. Patients with these risk factors should also be considered for prophylactic chemotherapy for the CNS.

Treatment Options by Clinical Stage

Treatment options for DLBCL differ between patients with localized (Ann Arbor stage I-II) and advanced (Ann Arbor stage III-IV) disease. Prognosis is extremely favorable for patients with no adverse risk factors (elevated LDH, stage II bulky disease, older than 60 years or ECOG performance status of 2 or more). Patients with advanced disease should be enrolled in clinical trials, whenever possible.

Stage I-II

In the SWOG 8736 study, 3 cycles of CHOP followed by involved field radiation therapy (IFRT) produced significantly better progression-free

survival (PFS; 5-year estimated PFS: 77% vs. 64% for CHOP alone) and OS (82% vs. 72% for CHOP alone) than 8 cycles of CHOP alone in patients with localized aggressive NHL;[17] however, this difference disappeared with further follow-up. The benefit of CHOP (3 cycles) followed by IFRT (5-year OS of 95%) in patients with limited-stage DLBCL (60 years or younger with no adverse risk factors) was also confirmed in a series from the British Columbia Cancer Agency.[18] Another randomized trial (ECOG 1484 study) showed that the addition of RT to CHOP (8 cycles) prolonged disease-free survival (DFS) in patients with limited stage DLBCL who had achieved CR to CHOP alone (6-year DFS was 73% for IFRT and 56% for observation).[19] In the GELA study (LNH 93-4), the addition of RT to 4 cycles of CHOP did not provide any advantage over 4 cycles of CHOP alone for the treatment of elderly patients with low-risk localized aggressive lymphoma. The estimated 5-year event-free survival (EFS) was not different between the two groups (61% and 64%, respectively) and the 5-year estimated OS rate was 68% and 72%, respectively.[20] However, in this study, administration of RT was markedly delayed and 12% of patients on the RT arm did not receive RT.

The efficacy of the addition of rituximab to CHOP (R-CHOP) and IFRT has also been reported in patients with limited stage DLBCL. In the SWOG 0014 study that evaluated 3 cycles of R-CHOP followed by IFRT in patients with at least one adverse factor (non-bulky stage II disease, age > 60 years, performance status of 2, or elevated serum LDH) as defined by the stage-modified IPI (N=60), the 4-year PFS rate was 88%, after a median follow-up of 5 years; the corresponding 4-year OS rate was 92%.[21] In historical comparison, these results were favorable relative to the survival rates for patients treated without rituximab (4-year PFS and OS were 78% and 88%, respectively). The MabThera International Trial (MInT) evaluated the role of rituximab in a phase 3

trial comparing 6 cycles of CHOP-like chemotherapy to 6 cycles of CHOP-like chemotherapy plus rituximab.[22,23] All patients were under the age of 60 years and had 0-1 IPI risk factors. Three quarters of patients had limited stage disease, and RT was included for all extranodal sites of disease or any site greater than 7.5 cm. The trial found a benefit to rituximab-containing chemotherapy with a 6-year OS rate of 90.1%% versus 80% (*P* = .0004). The 6-year EFS rate (74.3% vs. 55.8%; *P* < .0001) and PFS rate (80.2% vs. 63.9%; *P* < .0001) were also significantly higher for patients assigned to chemotherapy plus rituximab compared to chemotherapy alone.[23] In the two GELA studies, intensified chemotherapy [ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone) followed by consolidation with methotrexate, etoposide, ifosfamide and cytarabine] with or without rituximab was found to be superior to CHOP with or without rituximab (3 cycles) plus RT in patients with low-risk early-stage disease.[24,25] However, this regimen was also associated with significant toxicity and includes vindesine, which is not available in the United States.

Stage III-IV
R-CHOP-21 chemotherapy has been the standard treatment for patients with advanced stage DLBCL based on the results of the GELA study (LNH98-5) that demonstrated the addition of rituximab to CHOP-21 improved PFS and OS in elderly patients with advanced DLBCL. In this study, elderly patients (age 60–80 years; N=399) were randomized to receive 8 cycles of R-CHOP or CHOP.[26-28] Long-term follow-up of this study showed that PFS (36.5% vs. 20%), DFS (64% vs. 43%), and OS (43.5% vs. 28%) rates were significantly in favor of R-CHOP at a median follow-up of 10 years.[29] These findings have been confirmed in three additional randomized trials including the MabThera International Trial (MInT; 6 cycles of R-CHOP or CHOP) which extended the findings to young patients with 0 or 1 risk factors according to the IPI,[22,23] the Dutch HOVON and Nordic Lymphoma

group study (8 cycles of R-CHOP-14 or CHOP-14) and the ECOG/CALGB study confirming the findings in patients older than 60 years.[30,31] The ECOG/CALGB 9703 study also showed that maintenance rituximab in first remission offered no clinical benefit to patients who received R-CHOP as their induction therapy.[31]

The German High Grade Study Group demonstrated that 6 cycles of dose dense CHOP (CHOP-14) as first-line therapy was superior to 6 cycles of CHOP-21, prior to the introduction of rituximab.[32-34] In the RICOVER 60-trial, the addition of rituximab to 6 or 8 cycles of CHOP-14 (R-CHOP-14) significantly improved clinical outcomes in elderly patients (age 61–80 years) compared to CHOP-14 alone.[35,36] With a median observation time of 82 months, EFS was significantly improved after R-CHOP-14 (P <.001) compared with CHOP-14. OS rate was also significantly improved in R-CHOP-14 treated patients. No difference in clinical benefit but increased toxicity was seen in patients treated with 8 cycles compared with 6 cycles of therapy.[36] The investigators concluded that 6 cycles of R-CHOP-14 in combination with 8 doses of rituximab should be the preferred regimen in this patient population.

Two randomized trials have now reported data comparing R-CHOP-21 with dose-dense R-CHOP-14.[37,38] A large phase III randomized trial involving 1080 patients with newly diagnosed DLBCL found no significant difference in either PFS or OS at a median follow up of 46 months.[37] The 2-year OS rate was 82.7% in the R-CHOP-14 arm and 80.8% in the R-CHOP-21 arm (P = ·3763). The corresponding 2-year PFS rates were 75·4% and 74·8%, respectively (P =·5907). Toxicity was similar, except for a lower rate of grade 3 or 4 neutropenia in the R-CHOP-14 arm (31% vs. 60%), reflecting that all patients in the R-CHOP-14 arm received primary growth factor prophylaxis with G-CSF whereas no primary prophylaxis was given with R-CHOP-21.[37]

Notably, there was no difference in outcome between GCB-like and non-GCB-like DLBCL by IHC in this large prospective study. The phase III LNH03-6B GELA study compared 8 cycles of R-CHOP-14 with R-CHOP-21 in 602 elderly patients (age 60–80 years) with untreated DLBCL. After a median follow-up of 56 months, no significant differences between R-CHOP-14 and R-CHOP-21 were observed in terms of 3-year EFS (56% vs. 60%; P =.7614), PFS (60% vs. 62%) or OS rates (69% vs 72%).[38] Grade 3 or 4 neutropenia were observed more frequently in the R-CHOP-14 arm (74% compared to 64% in the R-CHOP 21 arm) despite a higher proportion of patients having received G-CSF (90%) compared with patients in the R-CHOP-21 arm (66%). Collectively, these studies suggest that R-CHOP-21 remains the standard treatment regimen for patients with newly diagnosed DLBCL with no improvement in outcome observed for dose-dense therapy in the rituximab era.

Very elderly patients (over the age of 80 years) have not been represented in prospective clinical trials of R-CHOP and are usually not appropriate candidates for full-dose therapy. To address this, the GELA study group conducted a multicenter single-arm prospective phase II study evaluating the safety and efficacy of a decreased dose of CHOP with a conventional dose of rituximab (R-mini-CHOP) in 149 patients older than 80 years with DLBCL.[39] After a median follow-up of 20 months, the median OS and PFS were 29 months and 21 months respectively. The 2-year OS and PFS rates were 59% and 47% respectively. An update with extended follow-up reports the 4-year PFS and OS rates to be 41% and 49%, respectively.[40] Grade ≥3 neutropenia was the most frequent hematological toxicity observed in 59 patients. The guidelines have included R-miniCHOP as a treatment option for elderly patients older than 80 years.

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Dose-adjusted EPOCH plus rituximab (DA-EPOCH-R) has shown significant activity in untreated patients with DLBCL.[41,42] In a multicenter phase II CALGB study, DA-EPOCH-R (6–8 cycles) was evaluated in patients with previously untreated DLBCL (N=69; included patients with PMBL, n=10).[43] IPI score was high-intermediate risk in 19% and high risk in 21% of patients. After a median follow up of 62 months, the 5-year TTP was 81% and OS was 84% in all patients. The 5-year TTP rates among patients with low/low-intermediate, high-intermediate, and high risk IPI were 87%, 92%, and 54%, respectively (P =.0085); the 5-year OS in these subgroups were 95%, 92%, and 43%, respectively (P<.001).[43] The TTP rate was significantly higher in the subgroup with GC phenotype compared with non-GC phenotype (100% vs. 67%; P=.008); the GC phenotype was also associated with a higher 5-year OS rate (94% vs. 68%; P=0.04). High tumor proliferation index (Ki-67 ≥60%) was associated with significantly decreased TTP and OS only for the subgroup with non-GCB phenotype. Febrile neutropenia occurred in 36% (grade 4 in 7%) and no significant grade 4 non-hematologic toxicities were observed. The most common grade 3 non-hematologic toxicities included neuropathies (25%), fatigue (16%), and arrhythmia (6%).[43] An ongoing phase III randomized CALGB study (CALGB 50303) is evaluating DA-EPOCH-R compared with R-CHOP in untreated patients with DLBCL. Pending results of that study, there is insufficient evidence to recommend DA-EPOCH-R as standard initial therapy of newly-diagnosed DLBCL except in highly selected circumstances such as poor left-ventricular function, B-cell lymphoma unclassifiable with intermediate features between DLBCL and Burkitt lymphoma, and primary mediastinal B-cell lymphoma (PMBL), where it warrants consideration (see Discussion section below for PMBL).[44]

As mentioned earlier, standard treatments do not exist for patients with "double-hit" lymphomas with concurrent *MYC* rearrangement and t(14;18) translocation leading to *BCL2* rearrangement. These lymphomas are highly aggressive with poor outcomes with standard DLBCL regimens such as R-CHOP.[11,12] In a series of 193 patients with DLBCL uniformly treated with standard R-CHOP, the median OS (13 months vs. 95 months) and PFS (6 months vs. 95 months), 3-year PFS rate (46% vs. 65%: P=.012) and 3-year OS rate (46% vs. 75%; P=.002) were significantly lower in patients with "double-hit" lymphoma compared with those without double-hit lymphoma.[11] In another study with a longer follow-up, 5-year PFS and OS were 18% and 27%, respectively, in patients with "double-hit" DLBCL treated with R-CHOP.[12] These studies have also shown that high expressions of both MYC and BCL2 protein levels (assessed by IHC)—but not *MYC* or *BCL2* expression alone—were associated with significantly inferior outcomes after treatment with R-CHOP.[11,12] In the multivariate analysis that included IPI score and cell of origin, concurrent *MYC/BCL2* expression remained a significant independent predictor of poorer PFS and OS after R-CHOP.[11,12]

In a recent multicenter retrospective analysis of 106 patients (77% of patients had "double-hit" lymphomas characterized by *MYC* and *BCL2* rearrangements), R-EPOCH resulted in superior complete responses compared to R-CHOP (P = .01) or other intensive induction regimen (P = .07).[45] In addition, primary refractory disease occurred less frequently in patients treated with R-EPOCH compared to R-CHOP (P = .005) or other intensive indiction regimens (P = .03). Prospective studies are needed to evaluate the efficacy of R-EPOCH as well as other regimens and stem cell transplantation strategies in patients with "double-hit" lymphomas. Alternative treatment strategies are needed to improve outcomes in this poor-risk patient population.

NCCN Recommendations

For patients with non-bulky (<10 cm) stage I or II disease, R-CHOP (3 cycles) with IFRT or R-CHOP (6 cycles) with or without IFRT is recommended. IFRT is recommended for patients who are not candidates for chemotherapy. Patients with bulky disease (10 cm or greater) may be more effectively treated with 6 cycles of R-CHOP with or without locoregional RT (category 1).

For patients with advanced stage disease, treatment with R-CHOP-21 (category 1) is recommended. In selected cases, RT to bulky sites may be beneficial (category 2B). R-CHOP-21 is recommended as initial therapy; however, other comparable anthracycline-based regimens may also be acceptable in selected circumstances. Suggested alternate options include dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) plus rituximab (category 2B) or dose-dense R-CHOP-14 (category 3).

The NCCN Guidelines have included the following regimens as first-line therapy options for very frail patients or those with poor left ventricular function:

- R-miniCHOP (for frail patients over 80 years of age)[39,40]
- CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) + rituximab [46]
- CDOP (cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone) + rituximab [47-49]
- CNOP (cyclophosphamide, mitoxantrone, vincristine and prednisone) + rituximab [50-53]
- Dose adjusted EPOCH + rituximab[41,42]
- CEOP (cyclophosphamide, etoposide, vincristine, and prednisone) + rituximab[54]

Participation in clinical trials of new regimens is recommended, if available. In patients with bulky disease or impaired renal function, initial therapy should include monitoring and prophylaxis for tumor lysis syndrome.

Some patients are at increased risk for developing CNS relapse, including those with involvement of the paranasal sinus, testes, bone marrow with large cell lymphoma, or having two or more extranodal sites with elevated LDH.[55-58] Although the optimal management of these patients is still under investigation, the NCCN Guidelines currently recommend CNS prophylaxis with 4 to 8 doses of intrathecal methotrexate and/or cytarabine, or 3-3.5 g/m^2 of systemic methotrexate. For patients with concurrent presentation of parenchymal involvement of the CNS, systemic methotrexate (3–8 g/m^2) should be incorporated as part of the treatment plan; for patients with concurrent leptomeningeal disease, 4 to 8 doses of intrathecal methotrexate and/or liposomal cytarabine and/or 3 to 3.5 g/m^2 systemic methotrexate should be incorporated. When administering high-dose methotrexate, patients should be pre-treated with hydration and alkalinization, and then receive leucovorin rescue beginning 24 hours after the beginning of the methotrexate infusion. Renal and hepatic function must be monitored. Full recovery of blood counts should be confirmed prior to initiating the next cycle of R-CHOP. Systemic methotrexate with leucovorin rescue has been safely incorporated into R-CHOP-21, with methotrexate administered on day 15 of the 21-day R-CHOP cycle.[59]

Response Assessment and Follow-up Therapy

Interim restaging is performed to identify patients whose disease has not responded to or has progressed on induction therapy. PET scans may be particularly useful in determining whether residual masses represent fibrosis or viable tumor. A negative PET scan after 2 to 4

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cycles of induction chemotherapy has been associated with favorable outcomes in several studies.[60-63] In patients with aggressive lymphoma (N=90) treated with first-line anthracycline-based induction chemotherapy (with rituximab in 41% of cases), patients with negative PET scans (n=54) after 2 cycles of induction therapy had significantly higher 2-year EFS rate (82% vs. 43%; P<0.001) and OS rate (90% vs. 61%; P=0.006) compared with those who were PET-positive (n=36).[62] In another study in patients with aggressive lymphoma (N=103) treated with first-line CHOP or CHOP-like regimens (with rituximab in 49% of cases), the 5-year EFS rates were significantly higher for PET-negative patients (n=77) compared to PET-positive patients (n=22) following 4 cycles of induction therapy (80% vs. 36%; P<0.0001).[63] However, interim PET scan can produce false positive results and some patients treated with chemoimmunotherapy have a favorable long-term outcome despite a positive interim PET scan. In a prospective study that evaluated the significance of interim PET scans in patients with DLBCL (after 4 cycles of accelerated R-CHOP), only 5 of 37 patients with a positive interim PET scan had a biopsy demonstrating persistent disease; PFS outcome in patients who were interim PET-positive, biopsy-negative was identical to that in patients with a negative interim PET scan.[64] A more recent retrospective analysis (88 newly diagnosed patients with DLBCL treated with 6-8 cycles of R-CHOP) that evaluated the predictive value of interim PET scans on PFS also reported only a minor difference in the 2-year PFS rates between patients with a positive interim PET scan a negative interim PET scan; the 2 year PFS rates were 85% and 72% respectively.[65] Conversely, the end-of-treatment PET scan was highly predictive of PFS; the 2-year PFS rates 83% and 64% respectively for final PET-positive and PET-negative patients (P <.001).

Therefore, interim PET scan is not recommended to be used to guide changes in therapy. If treatment modifications are considered based on interim PET scan results, a repeat biopsy of residual masses is recommended to confirm true positivity. Patients who are receiving induction therapy should undergo evaluation prior to receiving RT, including all positive studies, after 3-4 cycles of chemotherapy. End of treatment restaging is performed upon completion of treatment. The optimal time to end of treatment restaging is not known. However, the panel recommends waiting for 6-8 weeks after completion of therapy before repeating PET scans.

Considerable debate remains with the routine use of imaging for surveillance in patients who achieve a CR after induction therapy. Although positive scans can help to identify patients with early asymptomatic disease relapse, false positive cases remain common and problematic, and may lead to unnecessary radiation exposure for patients as well as increased healthcare costs. In a study that evaluated the use of surveillance CT scans (at 3 and 12 months after completion of chemotherapy) in patients with DLBCL who achieved a CR with induction chemotherapy (N=117), 35 patients relapsed, and only 6% of these relapses were detected by follow-up CT scan in asymptomatic patients; 86% of cases of relapse were associated with development of new symptoms or signs of relapse.[66] The investigators therefore concluded that routine surveillance with CT scans had limited value in the detection of early relapse in patients with a CR following induction therapy. In a retrospective study evaluating the use of surveillance imaging in patients with relapsed aggressive lymphoma who had a CR to initial chemotherapy (N=108), 20% of relapses were detected by imaging in asymptomatic patients.[67] In the remaining 80% of cases, relapse was identified by clinical signs and/or symptoms. Moreover, the cases of relapse detected by imaging were more likely to represent a

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population of patients with low-risk disease based on age-adjusted IPI at the time of relapse.[67] Thus, routine imaging during remission may help to identify patients with more limited disease at the time of relapse, but has not been shown to improve ultimate outcome.

In a prospective study that evaluated the role of PET scans (at 6, 12, 18, and 24 months after completion of induction therapy) in patients with a CR after induction therapy for lymphomas, surveillance using PET scans was found to be useful for detecting early relapse.[68] Among the cohort of patients with aggressive lymphomas in this study (n=183), follow-up PET scans detected true relapses in 10% of patients at 6 months, 5% at 12 months, and 11% at 18 months; the rate of false-positive scans was low, at 1% (including cohorts of patients with indolent and aggressive NHL).[68] Inconclusive PET scans were obtained in 8 of 183 cases (4%), 6 of which were confirmed as relapses based on biopsy evaluation. In a retrospective study that evaluated the use of follow-up PET/CT scan in patients with DLBCL who achieved a CR after induction therapy (N=75), follow-up PET/CT scan detected relapse in 27 patients, of which 23 were confirmed as relapses based on biopsy evaluation; thus, the positive predictive value of PET/CT scan for detecting relapse was 0.85.[69] In this study, patient age (>60 years) and the presence of clinical signs of relapse were significant predictors of disease relapse.[69]

Data from more recent retrospective studies also suggest that routine surveillance with PET or CT scans is of limited utility in the detection of relapse in majority of patients with DLBCL. A study comparing the performance of surveillance PET scans in patients with DLBCL treated with CHOP alone versus R-CHOP, found higher false positive results in patients treated with R-CHOP (77% vs. 26%; P < .001).[70] Another study reported a positive predictive value of 56% for surveillance PET-CT scans in patients IPI score <3 compared with 80% for patients with IPI

score ≥3, suggesting that surveillance PET-CT has a very limited role in the majority of patients in CR after primary therapy.[71] Another recent multi-institutional retrospective study that evaluated the utility of surveillance scans in a prospective, cohort of 537 patients with DLBCL treated with anthracycline-based chemoimmunotherapy reported that post treatment surveillance scans detected DLBCL relapse prior to clinical manifestations only in 1.5% (8 out 537 patients) during a planned follow-up visit.[72]

In the absence of evidence demonstrating an improved outcome favoring routine surveillance imaging for the detection of relapse, the NCCN Guidelines do not recommend the use of PET or CT for routine surveillance for patients with stage I-II disease who have achieved a CR to initial therapy For patients with stage III-IV disease who achieve remission to initial therapy, the NCCN Guidelines recommend CT scans no more than once every 6 months for up to 2 years after completion of treatment, with no ongoing routine surveillance imaging after that time, unless it is clinically indicated. When surveillance imaging is performed, CT scan is preferred over PET/CT for the majority of patients.

Interim and End of Treatment Response Evaluation for Stage I-II

When the treatment plan involves RT after short course therapy, restaging should be undertaken prior to RT including repeat PET scan as the dose of RT will be influenced by the result (see *"Principles of RT"* in the Guidelines). For full course therapy, if interim restaging demonstrates response, the planned course of treatment is completed.

If the interim restaging demonstrates a PR, treatment with a higher dose of RT (see Guidelines section on "Principles of RT") is appropriate. Alternatively, a repeat biopsy can be obtained and if positive, the patient can proceed to second-line therapy followed by HDT/ASCR. It is appropriate to enroll patients with an interim PR on a clinical trial. The

choice between these two options is often made on clinical grounds. RT is appropriate for patients not eligible for HDT/ASCR. Higher dose RT is also a reasonable choice if there is a very good PR. Patients with refractory or primarily progressive disease are managed as refractory or relapsed disease.

End of treatment restaging is performed upon completion of treatment. Imaging scans for restaging should be obtained at least 6 to 8 weeks after the completion of treatment. After end of treatment restaging, follow-up at regular intervals (every 3–6 months for 5 years and then annually or as clinically indicated thereafter) is recommended for patients with CR. In these patients, follow-up CT scans are recommended only if clinical indicated. Patients with PR and those with no response to treatment or progressive disease are treated as described for relapsed or refractory disease.

Interim and End of Treatment Response Evaluation for Stage III-IV
If interim staging (after 2–4 cycles of R-CHOP-21) demonstrates a CR and PR, the planned course of R-CHOP to a total of 6 cycles is completed. End of treatment restaging is performed upon completion of treatment. Imaging scans for restaging should be obtained approximately 6 to 8 weeks after the completion of treatment. Observation is preferred for patients with CR. RT to initially bulky disease (category 2B) or first-line consolidation with HDT/ASCR can be considered in selected high-risk patients (category 2B, see next section on Role of HDT/ASCR Consolidation in First Remission). Patients in CR are followed up at regular intervals (every 3–6 months for 5 years and then annually or as clinically indicated thereafter). In these patients, follow-up imaging CT scans should be performed no more than every 6 months for 2 years after completion of therapy, and then only as clinically indicated thereafter. Patients with PR (after completion of initial therapy) and those with no response to treatment

or progressive disease are treated as described below for relapsed or refractory disease.

Role of HDT/ASCR Consolidation in First Remission
In the randomized GELA LNH87-2 study, patients with DLBCL in first CR after induction therapy received consolidation therapy with either sequential chemotherapy or HDT/ASCR.[73] Although no difference in outcome was prospectively observed in this trial, a retrospective subset analysis of patients with aaIPI high/intermediate- or high-risk disease (n=236), found that HDT/ASCR resulted in significantly improved outcomes compared with sequential chemotherapy with regards to both 8-year disease-free survival rate (55% vs. 39%; *P*=0.02) and 8-year OS rate (64% vs. 49%; *P*=0.04) in the high-intermediate/high-risk subset.[73] This study was performed prior to rituximab-containing induction chemotherapy.

Recently, several randomized trials have prospectively evaluated the role of upfront HDT/ASCR after rituximab-containing first-line chemoimmunotherapy. In the French GOELAMS 075 study, patients aged ≤60 years with DLBCL (N=286 evaluable) were randomized to receive 8 cycles of R-CHOP-14 or HDT with rituximab (R-HDT) followed by ASCR.[74] The 3-year PFS rate and OS rate was 76% and 83%, respectively with no significant differences between treatment arms.[74] In a randomized trial of the German High-Grade NHL Study Group, patients aged ≤60 years with aggressive lymphomas (N=262 evaluable) were treated with 8 cycles of CHOEP-14 combined with 6 doses of rituximab (R-CHOEP-14) or 4 cycles of MegaCHOEP combined with 6 doses of rituximab and followed by ASCR (R-MegaCHOEP).[75] No significant differences were observed between the R-CHOEP-14 and R-MegaCHOEP arms for PFS (3-year rate: 74% vs. 70%, respectively) or OS outcomes (3-year rate: 85% vs. 77%, respectively). Among patients with high/intermediate aaIPI (score of 2), EFS (75.5% vs.

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63.5%; *P* = .0509) and OS rates (91% vs. 77.1%; *P* = .01) were significantly better with R-CHEOP-14 compared with R-MegaCHOEP.[75]

In the randomized DLCL04 trial of the Italian Lymphoma Foundation, patients aged ≤65 years with DLBCL, 399 patients were randomized to receive rituximab-containing first-line regimens (8 cycles of R-CHOP-14 or 6 cycles of R-MegaCHOP-14) with or without HDT/ASCR.[76] The 3-year PFS rate was significantly higher in the HDT/ASCR groups compared with the non-HDT/ASCR groups (70% vs. 59%; *P*=.010), but the 3-year OS rate was not significantly different between the two groups (81% and 78% respectively; *P* = .556). In addition, no significant differences were observed in the 3-year PFS rates between the two rituximab-based first-line regimens. In the SWOG 9704 trial, patients with high-intermediate/high IPI DLBCL were randomized (N=253) to receive 3 cycles of R-CHOP or HDT/ASCR, following initial remission with 5 cycles of CHOP or R-CHOP induction.[77] The 2-year PFS rate was significantly higher with HDT/ASCR compared with chemoimmunotherapy alone (69% vs. 56%; *P*=0.005); the 2-year OS rates were not significantly different (74% vs. 71%, respectively). On retrospective subset analysis of high IPI patients, however, an OS benefit was observed; in this subgroup, the 2-year PFS rate with HDT/ASCR was 75% compared with 41% with chemoimmunotherapy; the 2-year OS rate was 82% and 63%, respectively.[77]

The above studies, overall, found no benefit to upfront HDT/ASCR as compared with first-line rituximab-based chemoimmunotherapy. The suggestion of benefit limited to high-IPI risk patients warrants further prospective evaluation. Presently, upfront HDT/ASCR is recommended only in selected high-risk circumstances (category 2B), or in the context of a clinical trial.

Relapsed or Refractory Disease

The role of HDT/ASCR in patients with relapsed or refractory disease was demonstrated in an international randomized phase III trial (PARMA study).[78] In this study, patients with DLBCL responding to induction DHAP (dexamethasone, cisplatin and cytarabine) chemotherapy after first or second relapse (N=109) were randomized to receive additional DHAP chemotherapy plus RT or RT plus HDT/ASCR. The 5-year EFS rate was significantly higher among the transplant group compared with the non-transplant group (46% vs. 12%; *P*=.001), as was the 5-year OS (53% vs. 32%; *P*=.038).[78] This study was performed prior to the availability of rituximab. A recent retrospective analysis based on data from the EBMT registry evaluated the role of HDT/ASCR in patients achieving a second CR after salvage therapy (N=470).[79] In this analysis 25% of patients had received rituximab-containing therapy prior to ASCR. The 5-year DFS and OS was 48% and 63% after ASCR for all patients. The median DFS after ASCR was 51 months, which was significantly longer than the duration of first CR (11 months; *P*<.001). The longer DFS with ASCR compared with first CR was also significant in the subgroup of patients previously treated with rituximab (median not reached vs. 10 months; *P*<.001) and the subgroup who relapsed within 1 year of first-line therapy (median 47 months vs. 6 months; *P*<.001).[79]

The efficacy of second-line therapy is predicted by the second-line age-adjusted IPI.[80,81] Furthermore, pre-transplantation PET scans have been identified as predictive factors following HDT/ ASCR.[82,83] PET positivity before transplant and chemoresistance are associated with a poor outcome.[84,85] The results of studies from the GEL-TAMO group and ABMTR suggested that HDT/ASCR should be considered for patients who do not achieve a CR but who are still sensitive to chemotherapy.[86-88]

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Several chemotherapy regimens have been evaluated as second-line therapy prior to HDT/ASCR in patients with relapsed or refractory DLBCL.[89-94] However, none of these have emerged as a preferred regimen. In an outpatient setting, rituximab in combination with ifosfamide, carboplatin and etoposide (R-ICE) produced an ORR of 71% (25% CR) and an estimated 1-year EFS rate and OS rate of 60% and 72%, respectively, in patients with refractory B-cell lymphoma (N=28).[92] In a phase II study, R-ICE regimen produced a CR rate of 53% in patients with relapsed or refractory DLBCL (N=34), which was significantly better than historical controls treated with ICE alone (27%).[93] Rituximab in combination with gemcitabine-based chemotherapy regimens has also been shown to be effective in patients with relapsed or refractory DLBCL.[95-98] Rituximab as a single agent is modestly active in patients with relapsed or refractory DLBCL and is reserved for the frail elderly patient.[99]

An international randomized intergroup study (CORAL study; N=477) evaluated second-line therapy of relapsed or refractory DLBCL with R-ICE versus R-DHAP, followed by ASCR in all chemosensitive patients.[100,101] No significant difference in outcome was found between treatment arms. The overall response rates were 63% after R-ICE and 64% after R-DHAP. The 4-year EFS rate was 26% with R-ICE compared with 34% with R-DHAP (*P = .2*) and the 4-year OS rate was 43% and 51%, respectively (*P = .3*).[101] Thus, both regimens remain acceptable options for patients with relapsed or refractory DLBCL. Notably, patients relapsing less than 1 year after initial R-CHOP therapy had a particularly poor outcome with 3-year PFS of 23%. Moreover, the subgroup of patients with *MYC* rearrangements (with or without concurrent rearrangements in *BCL2* and/or *BCL6*) had poor outcomes regardless of treatment arm.[102] The 4-year PFS was 18% among patients with *MYC* rearrangements compared with 42% in those without

(*P*=.032); 4-year OS was 29% and 62%, respectively (*P*=.011). Among patients with *MYC* rearrangements, the 4-year PFS was 17% with R-DHAP and 19% with R-ICE; OS was 26% and 31%, respectively.[102] Novel approaches are needed for these poor-risk patients. Interestingly, a subgroup analysis from the CORAL study (Bio-CORAL) showed that for patients with a GC phenotype (based on Hans algorithm), R-DHAP resulted in improved PFS (3-year PFS 52% vs. 31% with R-ICE).[103] This difference was not observed among patients with non-GC phenotype (3-year PFS 32% with R-DHAP vs. 27% with R-ICE).[103]

The CORAL study was also designed to evaluate the role of rituximab maintenance (every 2 months for 1 year) following ASCR. Among the patients randomized post-ASCR to rituximab maintenance or observation (n=242), the 4-year EFS (after ASCR) was similar between randomized groups: 52% with rituximab versus 53% with observation.[101] The proportion of patients with progression or relapse was similar between randomized groups. In addition, the 4-year OS was not statistically different (61% and 65%, respectively). Serious adverse events were more frequent in the rituximab maintenance arm. Given that this study showed no benefit with rituximab maintenance compared with observation post-ASCR, maintenance therapy cannot be recommended in this setting.[101]

For patients with relapsed/refractory DLBCL not eligible for transplant, or relapsed after transplant, bendamustine in combination with rituximab (BR) has been evaluated in several studies with encouraging results. In a small dose-escalation study of BR in patients with relapsed/refractory aggressive NHL (N=9; DLBCL, n=5), the 90 mg/m^2 dose of bendamustine (n=3) in the BR regimen resulted in PR in 1 patient while the 120 mg/ m^2 dose of bendamustine (n=6) resulted in CRs in 5 patients and a PR in 1 patient.[104] In elderly patients with relapsed/refractory DLBCL (59 patients; median age 74 years; 48

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evaluable patients), the BR combination (with bendamustine dose 120 mg/m^2) resulted in an ORR of 45.8% (15.3% CR; 30.5% PR).[105] The median duration of response and median PFS were 17.3 months and 3.6 months respectively. Myelosuppression was the most common grade 3 or 4 toxicity. In a recent phase II study of the BR regimen (with bendamustine dose 120 mg/m^2) in patients with relapsed/refractory DLBCL (N=59; median age 67 years), the ORR was 63% with a CR in 37% of patients.[106] Patients had received 1 to 3 prior therapies, and were not considered suitable for (or have undergone) ASCR. Nearly all patients (97%) had received prior therapy with rituximab-containing regimens.[106] The median PFS with the BR regimen was approximately 7 months. The most common grade 3 or 4 toxicities were myelotoxicities including neutropenia (76%) and thrombocytopenia (22%).[106]

The regimen of rituximab, gemcitabine and oxaliplatin (R-GemOx) has also been evaluated in patients with relapsed or refractory DLBCL who are not eligible for transplant.[107-109] In a pilot study of 46 patients with relapsed or refractory B-cell lymphoma, the majority of whom (72%) had DLBCL, R-GemOx resulted in an ORR of 83% and half of the patients achieved a CR.[107] The 2-year EFS and OS rates in this study were 43% and 66%, respectively. In a subsequent multicenter phase II study that included 49 patients with relapsed or refractory DLBCL, R-GemOx resulted in an ORR of 61% (44% CR and 17% PR).[109] The 5-year PFS and OS rates were 12.8% and 13.9%, respectively.

NCCN Recommendations

HDT/ASCR is the treatment of choice for patients with relapsed or refractory disease that is chemosensitive at relapse. Patients with relapsed or refractory DLBCL who are candidates for HDT/ASCR should be treated with second-line chemotherapy, with or without rituximab (depending on whether the patient is deemed to be refractory

to prior rituximab regimens). Suggested regimens (with or without rituximab) include the following:

- DHAP (dexamethasone, cisplatin, cytarabine),
- ESHAP (methylprednisolone, etoposide, cytarabine, cisplatin)
- GDP (gemcitabine, dexamethasone, cisplatin)
- GemOx (gemcitabine and oxaliplatin)
- ICE (ifosfamide, carboplatin and etoposide)
- MINE (mitoxantrone, ifosfamide, mesna, etoposide)

Patients with CR or PR to second-line chemotherapy regimen should be considered for further consolidation with HDT/ASCR (category 1 for patients with CR) with or without RT. IFRT before HDT/ASCR has been shown to result in good local disease control and improved outcome.[110] Additional RT can be given before or after stem cell rescue to sites with prior positive disease. Pertinent clinical trials, including the option of allogeneic stem cell transplantation, may also be considered.

Patients who are not eligible for HDT/ASCR should be treated in the context of a clinical trial. Alternatively, in the absence of suitable clinical trials, patients can also be treated with single-agent rituximab, bendamustine with or without rituximab,[111] lenalidomide (in patients with non-germinal center DLBCL) with or without rituximab[112-116] or multiagent chemotherapy regimens (with or without rituximab) such as dose-adjusted EPOCH,[117,118] CEPP (cyclophosphamide, etoposide, prednisone and procarbazine),[46] GDP [95,119] or GemOx.[107-109]

Patients with disease relapse following HDT/ ASCR should be treated in the context of a clinical trial or treatment should be individualized. However, those with progressive disease after three successive regimens are unlikely to derive additional benefit from currently available chemotherapy regimens, except for patients who have

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experienced a long disease-free interval. All patients with relapsed or refractory DLBCL should be considered for enrollment in available clinical trials.

Primary Mediastinal Large B-cell Lymphoma (PMBL)

PMBL is a distinct subtype of NHL that histologically can be indistinguishable from DLBCL. This subtype tends to occur in young adults with a median age of 35 years with a slight female predominance.[120,121] PMBL arises from thymic B-cells with initial local regional spread to supraclavicular, cervical, hilar nodes and into the mediastinum and lung.[120] Widespread extranodal disease is uncommon at initial diagnosis, present in approximately one quarter of patients, but can be more common at recurrence.[121] Clinical symptoms related to rapid growth of mediastinal mass include superior vena cava (SVC) syndrome, pericardial and pleural effusions.

Gene expression profiling has indicated that PMBL is distinct from DLBCL; the pattern of gene expression in PMBL is more similar to classical Hodgkin lymphoma (CHL).[122,123] PMBL expresses B-cell antigens and lacks surface immunoglobulins. PMBL is CD19+, CD20+, CD22+, CD21-, IRF4/MUM1+ and CD23+ with a variable expression of BCL2 and BCL6. CD30 is weakly and heterogeneously expressed in more than 80% of cases and CD15 is occasionally present.[121] CD10 positivity is seen in 8-32% cases. PMBL is also characterized by a low expression of HLA I or II molecules. There have been rare cases of mediastinal gray zone lymphomas with combined features of PMBL and CHL. Cytogenetic abnormalities that are common in PMBL include gains in chromosome 9p24 (involving the *JAK2* in 50–75% of patients) and chromosome 2p15 (involving the *c-REL*, encoding a member of the NF-κB family of transcription factors) and loss in chromosomes 1p, 3p, 13q, 15q, and 17p.[121] Age-adjusted IPI is of limited value in determining

the prognosis of PMBL at diagnosis.[120,124,125] In a retrospective analysis of 141 patients from MSKCC, two or more extranodal sites and the type of initial therapy were predictors of outcome for EFS, whereas only the initial therapy was a predictor for OS.[124]

In retrospective analyses, intensive chemotherapy regimens have appeared more effective than CHOP[125-127] and the addition of IFRT has been associated with improved PFS; however, these studies were conducted in the pre-rituximab era.[128,129] The role of RT requires confirmation in prospective randomized trials. In a retrospective study, the addition of rituximab to MACOP-B or VACOP-B did not appear to result in significant differences in clinical outcomes, but it did appear to improve outcome when added to CHOP.[125,130-132]

A retrospective analysis of 63 patients with PMBL treated with R-CHOP found a 21% rate of primary induction failure, with adverse predictors of outcome being advanced stage and high-risk IPI scores. These data question whether R-CHOP is the optimal chemotherapy backbone in PMBL, particularly for high-risk patients.[133] A small prospective NCI study of the dose-adjusted EPOCH-R regimen (DA-EPOCH-R) without RT demonstrated an encouraging 91% EFS at a median follow-up of 4 years. In a subsequent prospective phase II study from the NCI, DA-EPOCH-R (6–8 cycles) and filgrastim, without RT, was evaluated in 51 patients with previously untreated PMBL.[44] Stage IV disease was present in 29% of patients. After DA-EPOCH-R therapy, 2 patients showed persistent focal disease and 1 patient had disease progression; 2 of these patients required mediastinal RT while 1 patient was observed after excision biopsy. At a median follow up of 63 months, EFS and OS rates were 93% and 97%, respectively. Grade 4 neutropenia and thrombocytopenia occurred in 50% and 6% of treatment cycles, respectively. Hospitalization for febrile neutropenia occurred in 13% of cycles.[44] This study showed that DA-EPOCH-R is a

highly effective regimen in patients with PMBL and obviates the need for RT in the large majority of patients. These observations will ideally be confirmed in larger prospective studies.

In an analysis of the subgroup of patients with PMBL (N=87) from the randomized MInT study, which evaluated CHOP-like regimens with or without rituximab, the addition of rituximab significantly improved the CR rate (80% vs. 54% without rituximab; *P*=.015) and 3-year EFS rate (78% vs. 52%; *P*=.012), but not the OS rate (89% vs. 78%; *P* = .158).[131] In a recent follow-up report with a median observation time of 62 months in patients with PMBL, the increase in EFS with rituximab remained significant at 5 years (79% vs. 47%; *P*=.011).[134] The 5-year PFS was also significantly increased in the rituximab arm (90% vs. 60%; *P*=.006); 5-year OS was not significantly different (90% vs. 78%), but was similar to OS outcomes in patients with DLBCL in this study (92% with rituximab vs. 81% without; *P*<.001).[134] The MInT study, however, only included young low-risk patients with IPI scores 0-1. Sequential dose dense R-CHOP followed by ICE consolidation (without RT) was also highly effective in patients with PMBL, with similar outcomes to the above analysis with R-chemotherapy from the MInT study.[135] At a median follow up for surviving patients at 3 years, the OS and PFS rates were 88% and 78%, respectively.[135]

In the absence of randomized trials, optimal first-line treatment for patients with PMBL is more controversial than other subtypes of NHL. However, based on the available data, the following regimens are included as options for first-line therapy.

- R-CHOP (6 cycles) + RT
- Dose-adjusted R-EPOCH (6 cycles)[44] + RT for persistent local disease

- R-CHOP (4 cycles) followed by ICE (3 cycles)[135] with or without RT (category 2B)

Post-treatment PET-CT is considered essential; if PET-CT is negative at the end of treatment and initial disease was non-bulky, patients may be observed. Residual mediastinal masses are common. For patients initially treated with R-CHOP, consolidation with RT can be considered, particularly if increased FDG-activity persists in the primary tumor. For patients who are PET-CT negative after more intensive therapies (e.g., dose-adjusted EPOCH-R), observation may be appropriate. If PET-CT is positive, biopsy is recommended if additional treatment is contemplated.

Grey Zone Lymphoma

Grey zone lymphomas refer to a group of lymphomas with overlapping histological and clinical features representative of different lymphoma subtypes.[136] In the context of large B-cell lymphomas, grey zone lymphomas fall under the category of "B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma (CHL) of the 2008 WHO classification.[134,136-138] Other synonyms include large B-cell lymphoma with Hodgkin features or Hodgkin-like anaplastic large cell lymphoma. Patients with gray zone lymphomas may present with mediastinal or non-mediastinal disease. Clinically, patients with mediastinal grey zone lymphomas present with large anterior mediastinal mass with or without supraclavicular lymph node involvement. These mediastinal lymphomas are more commonly seen in young adult males between the ages of 20 to 40 years.[136,137,139] Patients with non-mediastinal gray zone lymphoma tended to be older and have a higher incidence of advanced stage disease and high-risk IPI score than their mediastinal counterparts.[140] The morphology of grey zone lymphomas is characterized by sheet-like growth of pleomorphic cells in a diffusely fibrous stroma; cells are typically larger

and more pleomorphic than those in PMBL, and may sometimes resemble lacunar or Hodgkin-like cells.[138] Necrosis without neutrophilic infiltration is frequently present.[134,137,138]

The immunophenotype is atypical, often showing transitional features between PMBL and CHL. In general, CD45 is often positive, and CD15, CD20, CD30, and CD79a are also frequently positive. CD10 and ALK are usually negative. B-cell transcription factors such as PAX5, BOB.1, and OCT-2 are often positive.[137,138,141] BCL6 is variably expressed. EBV is more often negative.[136,137] If the morphology more closely resembles PMBL, absence of CD20, CD15 positivity, or presence of EBV would be suggestive of grey zone lymphoma. If the morphology more closely resembles CHL, strong CD20 expression (and/or other B-cell markers) and absence of CD15 would be suggestive of grey zone lymphoma.[137] A study that evaluated epigenetic changes based on DNA methylation analysis of microdissected tumor cells from patients with mediastinal grey zone lymphomas, PMBL, CHL, and DLBCL showed distinct methylation signatures (hypomethylated and hypermethylated sites) of CpG targets between PMBL and CHL.[142] The methylation profiles of patients with grey zone lymphoma were intermediate to those of PMBL and CHL, but distinct from patients with DLBCL. Among 235 CpG targets that were identified as being differentially methylated between the lymphomas, 22 targets could be used to readily distinguish between PMBL and CHL cases, with grey zone lymphomas showing an overlap of both signatures. The investigators concluded that the unique epigenetic signature of mediastinal grey zone lymphomas provide validation of its classification as a separate disease entity in the 2008 WHO classification.[142]

The treatment of patients with grey zone lymphomas poses a challenge, as these lymphomas appear to be associated with a worse prognosis compared with PMBL or CHL.[138,141,143] No standard of care or consensus exists for the management of patients with grey zone lymphomas, although patients are typically treated with multiagent chemotherapy regimens used for patients with DLBCL with the addition of RT for localized disease; some reports suggest that grey zone lymphomas tend to be resistant to chemotherapy regimens used in CHL.[139,144] The addition of rituximab is generally suggested for tumors expressing CD20. In a study that evaluated 6 to 8 cycles of DA-EPOCH-R in a small group of patients with mediastinal grey zone lymphoma (n=11), the 4-year PFS was 30% and 4-year OS was 83%.[144] These outcomes appeared to be poorer compared with the group of patients with PMBL (n=35) in the same study; the 4-year PFS and OS rates were 100% for both endpoints in patients with PMBL treated with DA-EPOCH-R. Moreover, half of the patients with grey zone lymphoma required mediastinal RT.[144] Given the apparent inferior outcomes among gray zone lymphomas treated with traditional chemotherapy regimens, consolidative RT should be strongly considered for patients with limited stage disease amenable to RT.

Patients with grey zone lymphomas are best managed in cancer centers with experience in treating this type of lymphoma, preferably in the context of clinical trials where appropriate. In the absence of suitable clinical trials, an intensive regimen such as DA-EPOCH-R (with mediastinal RT, as needed, for local disease) may be considered.

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NCCN Guidelines Version 4.2014
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References

1. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 1997;89:3909-3918. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9166827.

2. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 2000;403:503-511. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10676951.

3. Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood 2004;103:275-282. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14504078.

4. Choi WWL, Weisenburger DD, Greiner TC, et al. A new immunostain algorithm classifies diffuse large B-cell lymphoma into molecular subtypes with high accuracy. Clin Cancer Res 2009;15:5494-5502. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19706817.

5. Meyer PN, Fu K, Greiner TC, et al. Immunohistochemical methods for predicting cell of origin and survival in patients with diffuse large B-cell lymphoma treated with rituximab. J Clin Oncol 2011;29:200-207. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21135273.

6. Savage KJ, Johnson NA, Ben-Neriah S, et al. MYC gene rearrangements are associated with a poor prognosis in diffuse large B-cell lymphoma patients treated with R-CHOP chemotherapy. Blood 2009;114:3533-3537. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19704118.

7. Barrans S, Crouch S, Smith A, et al. Rearrangement of MYC is associated with poor prognosis in patients with diffuse large B-cell lymphoma treated in the era of rituximab. J Clin Oncol 2010;28:3360-3365. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20498406.

8. Aukema SM, Siebert R, Schuuring E, et al. Double-hit B-cell lymphomas. Blood 2011;117:2319-2331. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21119107.

9. Snuderl M, Kolman OK, Chen YB, et al. B-cell lymphomas with concurrent IGH-BCL2 and MYC rearrangements are aggressive neoplasms with clinical and pathologic features distinct from Burkitt lymphoma and diffuse large B-cell lymphoma. Am J Surg Pathol 2010;34:327-340. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20118770.

10. Le Gouill S, Talmant P, Touzeau C, et al. The clinical presentation and prognosis of diffuse large B-cell lymphoma with t(14;18) and 8q24/c-MYC rearrangement. Haematologica 2007;92:1335-1342. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18024371.

11. Green TM, Young KH, Visco C, et al. Immunohistochemical double-hit score is a strong predictor of outcome in patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol 2012;30:3460-3467. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22665537.

12. Johnson NA, Slack GW, Savage KJ, et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol 2012;30:3452-3459. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22851565.

13. Bain BJ. Bone marrow trephine biopsy. J Clin Pathol 2001;54:737-742. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11577117.

14. Bishop PW, McNally K, Harris M. Audit of bone marrow trephines. J Clin Pathol 1992;45:1105-1108. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1479037.

15. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med 1993;329:987-994. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8141877.

16. Zhou Z, Sehn LH, Rademaker AW, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. Blood 2014;123:837-842. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24264230.

17. Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med 1998;339:21-26. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9647875.

18. Shenkier TN, Voss N, Fairey R, et al. Brief chemotherapy and involved-region irradiation for limited-stage diffuse large-cell lymphoma: an 18-year experience from the British Columbia Cancer Agency. J Clin Oncol 2002;20:197-204. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11773170.

19. Horning SJ, Weller E, Kim K, et al. Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-Hodgkin's lymphoma: Eastern Cooperative Oncology Group study 1484. J Clin Oncol 2004;22:3032-3038. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15210738.

20. Bonnet C, Fillet G, Mounier N, et al. CHOP alone compared with CHOP plus radiotherapy for localized aggressive lymphoma in elderly patients: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 2007;25:787-792. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17228021.

21. Persky DO, Unger JM, Spier CM, et al. Phase II study of rituximab plus three cycles of CHOP and involved-field radiotherapy for patients with limited-stage aggressive B-cell lymphoma: Southwest Oncology Group study 0014. J Clin Oncol 2008;26:2258-2263. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18413640.

22. Pfreundschuh M, Trumper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol 2006;7:379-391. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16648042.

23. Pfreundschuh M, Kuhnt E, Trumper L, et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. Lancet Oncol 2011;12:1013-1022. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21940214.

24. Reyes F, Lepage E, Ganem G, et al. ACVBP versus CHOP plus radiotherapy for localized aggressive lymphoma. N Engl J Med 2005;352:1197-1205. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15788496.

25. Recher C, Coiffier B, Haioun C, et al. Intensified chemotherapy with ACVBP plus rituximab versus standard CHOP plus rituximab for the treatment of diffuse large B-cell lymphoma (LNH03-2B): an open-label randomised phase 3 trial. Lancet 2011;378:1858-1867. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22118442.

26. Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 1993;328:1002-1006. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7680764.

27. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002;346:235-242. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11807147.

28. Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 2005;23:4117-4126. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15867204.

29. Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood 2010;116:2040-2045. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20548096.

30. Sonneveld P, van Putten W, Holte H, et al. Intensified CHOP with rituximab for intermediate or high-risk Non-hodgkin's lymphoma: interim analysis of a randomized phase III trial in elderly patients by the Dutch HOVON and Nordic Lymphoma Groups [abstract]. Blood 2005;106:Abstract 16. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/106/11/16.

31. Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol 2006;24:3121-3127. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16754935.

32. Blayney DW, LeBlanc ML, Grogan T, et al. Dose-intense chemotherapy every 2 weeks with dose-intense cyclophosphamide, doxorubicin, vincristine, and prednisone may improve survival in intermediate- and high-grade lymphoma: a phase II study of the Southwest Oncology Group (SWOG 9349). J Clin Oncol 2003;21:2466-2473. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12829664.

33. Halaas JL, Moskowitz CH, Horwitz S, et al. R-CHOP-14 in patients with diffuse large B-cell lymphoma: feasibility and preliminary efficacy. Leuk Lymphoma 2005;46:541-547. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16019482.

34. Pfreundschuh M, Trumper L, Kloess M, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL. Blood 2004;104:634-641. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15016643.

35. Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). Lancet Oncol 2008;9:105-116. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18226581.

36. Pfreundschuh M, Ziepert M, Zeynalova S, et al. Six versus eight cycles of biweekly CHOP-14 with or without R in elderly patients (pts) with aggressive CD20+ B-cell lymphomas: Seven-year FU of the RICOVER-60 trial of the DSHNHL [abstract 8029]. J Clin Oncol 2011;29:Abstract 8029. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/8029.

37. Cunningham D, Hawkes EA, Jack A, et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. Lancet 2013;381:1817-1826. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23615461.

38. Delarue R, Tilly H, Mounier N, et al. Dose-dense rituximab-CHOP compared with standard rituximab-CHOP in elderly patients with diffuse large B-cell lymphoma (the LNH03-6B study): a randomised phase 3 trial. Lancet Oncol 2013;14:525-533. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23578722.

39. Peyrade F, Jardin F, Thieblemont C, et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. Lancet Oncol 2011;12:460-468. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21482186.

40. Peyrade F, Fain O, Fabiani B, et al. Long-term follow-up of the GELA LNH 03-7B study: A prospective phase II study of 150 patients over 80 years with diffuse large B-cell lymphoma (DLBCL) treated with RminiCHOP [abstract]. J Clin Oncol 2013;31(15_suppl):Abstract 8536. Available at:
http://meeting.ascopubs.org/cgi/content/abstract/31/15_suppl/8536.

41. Purroy N, Lopez A, Vallespi T, et al. Dose-adjusted epoch plus rituximab (DA-EPOCH-R) in untreated patients with poor risk large B-cell lymphoma. A phase 2 study conducted by the Spanish PETHEMA Group [abstract]. Blood 2009;114:Abstract 2701. Available at:
http://abstracts.hematologylibrary.org/cgi/content/abstract/114/22/2701.

42. Wilson WH, Dunleavy K, Pittaluga S, et al. Phase II study of dose-adjusted EPOCH and rituximab in untreated diffuse large B-cell lymphoma with analysis of germinal center and post-germinal center biomarkers. J Clin Oncol 2008;26:2717-2724. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/18378569.

43. Wilson WH, Jung SH, Porcu P, et al. A Cancer and Leukemia Group B multi-center study of DA-EPOCH-rituximab in untreated diffuse large B-cell lymphoma with analysis of outcome by molecular subtype. Haematologica 2012;97:758-765. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/22133772.

44. Dunleavy K, Pittaluga S, Maeda LS, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. N Engl J Med 2013;368:1408-1416. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/23574119.

45. Petrich AM, Cassaday RD, Press OW, et al. Impact Of Induction Regimen and Consolidative Stem Cell Transplantation In Patients With Double Hit Lymphoma (DHL): A Large Multicenter Retrospective Analysis. Blood 2013;122:640. Available at:
http://bloodjournal.hematologylibrary.org/content/122/21/640.abstract.

46. Chao NJ, Rosenberg SA, Horning SJ. CEPP(B): an effective and well-tolerated regimen in poor-risk, aggressive non-Hodgkin's lymphoma. Blood 1990;76:1293-1298. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/2207307.

47. Martino R, Perea G, Caballero MD, et al. Cyclophosphamide, pegylated liposomal doxorubicin (Caelyx), vincristine and prednisone (CCOP) in elderly patients with diffuse large B-cell lymphoma: results from a prospective phase II study. Haematologica 2002;87:822-827. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12161358.

48. Visani G, Guiducci B, D'Adamo F, et al. Cyclophosphamide, pegylated liposomal doxorubicin, vincristine and prednisone (CDOP) plus rituximab is effective and well tolerated in poor performance status elderly patients with non-Hodgkin's lymphoma. Leuk Lymphoma 2005;46:477-479. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/15621843.

49. Zaja F, Tomadini V, Zaccaria A, et al. CHOP-rituximab with pegylated liposomal doxorubicin for the treatment of elderly patients with diffuse large B-cell lymphoma. Leuk Lymphoma 2006;47:2174-2180. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/17071492.

50. Bessell EM, Burton A, Haynes AP, et al. A randomised multicentre trial of modified CHOP versus MCOP in patients aged 65 years and over with aggressive non-Hodgkin's lymphoma. Ann Oncol 2003;14:258-267. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/12562653.

51. Bezwoda W, Rastogi RB, Erazo Valla A, et al. Long-term results of a multicentre randomised, comparative phase III trial of CHOP versus CNOP regimens in patients with intermediate- and high-grade non-Hodgkin's lymphomas. Novantrone International Study Group. Eur J Cancer 1995;31A:903-911. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/7646919.

52. Pangalis GA, Vassilakopoulos TP, Michalis E, et al. A randomized trial comparing intensified CNOP vs. CHOP in patients with aggressive non-Hodgkin's lymphoma. Leuk Lymphoma 2003;44:635-644. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12769340.

53. Sonneveld P, de Ridder M, van der Lelie H, et al. Comparison of doxorubicin and mitoxantrone in the treatment of elderly patients with advanced diffuse non-Hodgkin's lymphoma using CHOP versus CNOP chemotherapy. J Clin Oncol 1995;13:2530-2539. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7595704.

54. Moccia AA, Schaff K, Hoskins P, et al. R-CHOP with etoposide substituted for doxorubicin (R-CEOP): excellent outcome in diffuse large b cell lymphoma for patients with a contraindication to anthracyclines [abstract]. Blood 2009;114:Abstract 408. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/114/22/408.

55. Arkenau HT, Chong G, Cunningham D, et al. The role of intrathecal chemotherapy prophylaxis in patients with diffuse large B-cell lymphoma. Ann Oncol 2007;18:541-545. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17164228.

56. Laskin JJ, Savage KJ, Voss N, et al. Primary paranasal sinus lymphoma: natural history and improved outcome with central nervous system chemoprophylaxis. Leuk Lymphoma 2005;46:1721-1727. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16263574.

57. Shimazu Y, Notohara K, Ueda Y. Diffuse large B-cell lymphoma with central nervous system relapse: prognosis and risk factors according to retrospective analysis from a single-center experience. Int J Hematol 2009;89:577-583. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19353238.

58. Zucca E, Conconi A, Mughal TI, et al. Patterns of outcome and prognostic factors in primary large-cell lymphoma of the testis in a survey by the International Extranodal Lymphoma Study Group. J Clin Oncol 2003;21:20-27. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12506165.

59. Abramson JS, Hellmann M, Barnes JA, et al. Intravenous methotrexate as central nervous system (CNS) prophylaxis is associated with a low risk of CNS recurrence in high-risk patients with diffuse large B-cell lymphoma. Cancer 2010;116:4283-4290. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20564149.

60. Mikhaeel NG, Timothy AR, O'Doherty MJ, et al. 18-FDG-PET as a prognostic indicator in the treatment of aggressive Non-Hodgkin's Lymphoma-comparison with CT. Leuk Lymphoma 2000;39:543-553. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11342337.

61. Spaepen K, Stroobants S, Dupont P, et al. Early restaging positron emission tomography with (18)F-fluorodeoxyglucose predicts outcome in patients with aggressive non-Hodgkin's lymphoma. Ann Oncol 2002;13:1356-1363. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12196360.

62. Haioun C, Itti E, Rahmouni A, et al. [18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in aggressive lymphoma: an early prognostic tool for predicting patient outcome. Blood 2005;106:1376-1381. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15860666.

63. Dupuis J, Itti E, Rahmouni A, et al. Response assessment after an inductive CHOP or CHOP-like regimen with or without rituximab in 103 patients with diffuse large B-cell lymphoma: integrating 18fluorodeoxyglucose positron emission tomography to the International Workshop Criteria. Ann Oncol 2009;20:503-507. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19074215.

64. Moskowitz CH, Schoder H, Teruya-Feldstein J, et al. Risk-adapted dose-dense immunochemotherapy determined by interim FDG-PET in advanced-stage diffuse large B-cell lymphoma. J Clin Oncol 2010;28:1896-1903. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20212248.

65. Pregno P, Chiappella A, Bello M, et al. Interim 18-FDG-PET/CT failed to predict the outcome in diffuse large B-cell lymphoma patients

treated at the diagnosis with rituximab-CHOP. Blood 2012;119:2066-2073. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22234681.

66. Guppy AE, Tebbutt NC, Norman A, Cunningham D. The role of surveillance CT scans in patients with diffuse large B-cell non-Hodgkin's lymphoma. Leuk Lymphoma 2003;44:123-125. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12691151.

67. Liedtke M, Hamlin PA, Moskowitz CH, Zelenetz AD. Surveillance imaging during remission identifies a group of patients with more favorable aggressive NHL at time of relapse: a retrospective analysis of a uniformly-treated patient population. Ann Oncol 2006;17:909-913. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16672295.

68. Zinzani PL, Stefoni V, Tani M, et al. Role of [18F]fluorodeoxyglucose positron emission tomography scan in the follow-up of lymphoma. J Clin Oncol 2009;27:1781-1787. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19273712.

69. Petrausch U, Samaras P, Haile SR, et al. Risk-adapted FDG-PET/CT-based follow-up in patients with diffuse large B-cell lymphoma after first-line therapy. Ann Oncol 2010;21:1694-1698. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20139151.

70. Avivi I, Zilberlicht A, Dann EJ, et al. Strikingly high false positivity of surveillance FDG-PET/CT scanning among patients with diffuse large cell lymphoma in the rituximab era. Am J Hematol 2013;88:400-405. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23423884.

71. Cheah CY, Hofman MS, Dickinson M, et al. Limited role for surveillance PET-CT scanning in patients with diffuse large B-cell lymphoma in complete metabolic remission following primary therapy. Br J Cancer 2013;109:312-317. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23807169.

72. Thompson CA, Maurer MJ, Ghesquieres H, et al. Utility of post-therapy surveillance scans in DLBCL [abstract]. J Clin Oncol 2013;31:Abstract 8504. Available at: http://meeting.ascopubs.org/cgi/content/abstract/31/15_suppl/8504.

73. Haioun C, Lepage E, Gisselbrecht C, et al. Survival benefit of high-dose therapy in poor-risk aggressive non-Hodgkin's lymphoma: final analysis of the prospective LNH87-2 protocol--a groupe d'Etude des lymphomes de l'Adulte study. J Clin Oncol 2000;18:3025-3030. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10944137.

74. Le Gouill S, Milpied NJ, Lamy T, et al. First-line rituximab (R) high-dose therapy (R-HDT) versus R-CHOP14 for young adults with diffuse large B-cell lymphoma: Preliminary results of the GOELAMS 075 prospective multicenter randomized trial [abstract]. J Clin Oncol 2011;29:Abstract 8003. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/8003.

75. Schmitz N, Nickelsen M, Ziepert M, et al. Conventional chemotherapy (CHOEP-14) with rituximab or high-dose chemotherapy (MegaCHOEP) with rituximab for young, high-risk patients with aggressive B-cell lymphoma: an open-label, randomised, phase 3 trial (DSHNHL 2002-1). Lancet Oncol 2012;13:1250-1259. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23168367.

76. Vitolo U, Chiappella A, Brusamolino E, et al. Rituximab Dose-Dense Chemotherapy Followed by Intensified High-Dose Chemotherapy and Autologous Stem Cell Transplantation (HDC+ASCT) Significantly Reduces the Risk of Progression Compared to Standard Rituximab Dose-Dense Chemotherapy As First Line Treatment in Young Patients with High-Risk (aa-IPI 2-3) Diffuse Large B-Cell Lymphoma (DLBCL): Final Results of Phase III Randomized Trial DLCL04 of the Fondazione Italiana Linfomi (FIL). ASH Annual Meeting Abstracts 2012;120:688-. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;120/21/688.

77. Stiff PJ, Unger JM, Cook J, et al. Randomized phase III U.S./Canadian intergroup trial (SWOG S9704) comparing CHOP {+/-} R for eight cycles to CHOP {+/-} R for six cycles followed by

autotransplant for patients with high-intermediate (H-Int) or high IPI grade diffuse aggressive non-Hodgkin lymphoma (NHL) [abstract 8001]. J Clin Oncol 2011;29:Abstract 8001. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/8001.

78. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med 1995;333:1540-1545. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7477169.

79. Mounier N, Canals C, Gisselbrecht C, et al. High-dose therapy and autologous stem cell transplantation in first relapse for diffuse large B cell lymphoma in the rituximab era: an analysis based on data from the European Blood and Marrow Transplantation Registry. Biol Blood Marrow Transplant 2012;18:788-793. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22005647.

80. Hamlin PA, Zelenetz AD, Kewalramani T, et al. Age-adjusted International Prognostic Index predicts autologous stem cell transplantation outcome for patients with relapsed or primary refractory diffuse large B-cell lymphoma. Blood 2003;102:1989-1996. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12676776.

81. Lerner RE, Thomas W, Defor TE, et al. The International Prognostic Index assessed at relapse predicts outcomes of autologous transplantation for diffuse large-cell non-Hodgkin's lymphoma in second complete or partial remission. Biol Blood Marrow Transplant 2007;13:486-492. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17382255.

82. Derenzini E, Musuraca G, Fanti S, et al. Pretransplantation positron emission tomography scan is the main predictor of autologous stem cell transplantation outcome in aggressive B-cell non-Hodgkin lymphoma. Cancer 2008;113:2496-2503. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18833583.

83. Spaepen K, Stroobants S, Dupont P, et al. Prognostic value of pretransplantation positron emission tomography using fluorine 18-fluorodeoxyglucose in patients with aggressive lymphoma treated with high-dose chemotherapy and stem cell transplantation. Blood 2003;102:53-59. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12609836.

84. Trneny M, Bosly A, Bouabdallah K, et al. Independent predictive value of PET-CT pre transplant in relapsed and refractory patients with CD20 diffuse large B-cell lymphoma (DLBCL) included in the CORAL study [abstract]. Blood 2009;114:Abstract 881. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/114/22/881.

85. Hoppe BS, Moskowitz CH, Zhang Z, et al. The role of FDG-PET imaging and involved field radiotherapy in relapsed or refractory diffuse large B-cell lymphoma. Bone Marrow Transplant 2009;43:941-948. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19139730.

86. Caballero MD, Pérez-Simón JA, Iriondo A, et al. High-dose therapy in diffuse large cell lymphoma: results and prognostic factors in 452 patients from the GEL-TAMO Spanish Cooperative Group. Annals of Oncology 2003;14:140-151. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12488306.

87. Rodriguez J, Caballero MD, Gutierrez A, et al. Autologous stem-cell transplantation in diffuse large B-cell non-Hodgkin's lymphoma not achieving complete response after induction chemotherapy: the GEL/TAMO experience. Annals of Oncology 2004;15:1504-1509. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15367411.

88. Vose JM, Zhang MJ, Rowlings PA, et al. Autologous transplantation for diffuse aggressive Non-hodgkin's lymphoma in patients never achieving remission: a report from the autologous Blood and Marrow Transplant Registry. J Clin Oncol 2001;19:406-413. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11208832.

89. Velasquez WS, McLaughlin P, Tucker S, et al. ESHAP--an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year

follow-up study. J Clin Oncol 1994;12:1169-1176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8201379.

90. Joyce RM, Regan M, Ottaway J, et al. A phase I-II study of rituximab, ifosfamide, mitoxantrone and etoposide (R-IME) for B cell non-Hodgkin's lymphoma prior to and after high-dose chemotherapy and autologous stem cell transplantation (HDC-ASCT). Ann Oncol 2003;14 Suppl 1:21-27. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12736227.

91. Zelenetz AD, Hamlin P, Kewalramani T, et al. Ifosfamide, carboplatin, etoposide (ICE)-based second-line chemotherapy for the management of relapsed and refractory aggressive non-Hodgkin's lymphoma. Ann Oncol 2003;14 Suppl 1:i5-10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12736224.

92. Vose J, Sneller V. Outpatient regimen rituximab plus ifosfamide, carboplatin and etoposide (R-ICE) for relapsed non-Hodgkin's lymphoma. Ann Oncol 2003;14 Suppl 1:17-20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12736226.

93. Kewalramani T, Zelenetz AD, Nimer SD, et al. Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. Blood 2004;103:3684-3688. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14739217.

94. Mey UJ, Orlopp KS, Flieger D, et al. Dexamethasone, high-dose cytarabine, and cisplatin in combination with rituximab as salvage treatment for patients with relapsed or refractory aggressive non-Hodgkin's lymphoma. Cancer Invest 2006;24:593-600. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16982464.

95. Crump M, Baetz T, Couban S, et al. Gemcitabine, dexamethasone, and cisplatin in patients with recurrent or refractory aggressive histology B-cell non-Hodgkin lymphoma: a Phase II study by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG). Cancer

2004;101:1835-1842. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15386331.

96. Lopez A, Gutierrez A, Palacios A, et al. GEMOX-R regimen is a highly effective salvage regimen in patients with refractory/relapsing diffuse large-cell lymphoma: a phase II study. Eur J Haematol 2008;80:127-132. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18005385.

97. Moccia AA, Hitz F, Hoskins P, et al. Gemcitabine, dexamethasone, and cisplatin (GDP) is an effective and well-tolerated out-patient salvage therapy for relapsed/refractory diffuse large B-cell lymphoma (DLBCL) and Hodgkin lymphoma (HL). Blood 2010;116:113. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/113.

98. Cultrera JL, Liu J, Liboy I, et al. A Phase II study of gemcitabine, rituximab, and oxaliplatin in combination for relapsed/refractory non-hodgkin's lymphomas [abstract]. Blood 2010;116:Abstract 2879. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/2879.

99. Coiffier B, Haioun C, Ketterer N, et al. Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: a multicenter phase II study. Blood 1998;92:1927-1932. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9731049.

100. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era J Clin Oncol 2010;28:4184-4190. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20660832.

101. Gisselbrecht C, Schmitz N, Mounier N, et al. Rituximab Maintenance Therapy After Autologous Stem-Cell Transplantation in Patients With Relapsed CD20+ Diffuse Large B-Cell Lymphoma: Final Analysis of the Collaborative Trial in Relapsed Aggressive Lymphoma. J

Clin Oncol 2012;30:4462-4469. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/23091101.

102. Cuccuini W, Briere J, Mounier N, et al. MYC+ diffuse large B-cell lymphoma is not salvaged by classical R-ICE or R-DHAP followed by BEAM plus autologous stem cell transplantation. Blood 2012;119:4619-4624. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/22408263.

103. Thieblemont C, Briere J, Mounier N, et al. The germinal center/activated B-cell subclassification has a prognostic impact for response to salvage therapy in relapsed/refractory diffuse large B-cell lymphoma: a bio-CORAL study. J Clin Oncol 2011;29:4079-4087. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21947824.

104. Ogura M, Ando K, Taniwaki M, et al. Feasibility and pharmacokinetic study of bendamustine hydrochloride in combination with rituximab in relapsed or refractory aggressive B cell non-Hodgkin's lymphoma(6). Cancer Sci 2011;102:1687-1692. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21624007.

105. Vacirca JL, Acs PI, Tabbara IA, et al. Bendamustine combined with rituximab for patients with relapsed or refractory diffuse large B cell lymphoma. Ann Hematol 2014;93:403-409. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23955074.

106. Ohmachi K, Niitsu N, Uchida T, et al. Multicenter Phase II Study of Bendamustine Plus Rituximab in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma. J Clin Oncol 2013;31:2103-2109. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23650408.

107. El Gnaoui T, Dupuis J, Belhadj K, et al. Rituximab, gemcitabine and oxaliplatin: an effective salvage regimen for patients with relapsed or refractory B-cell lymphoma not candidates for high-dose therapy. Ann Oncol 2007;18:1363-1368. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17496309.

108. Corazzelli G, Capobianco G, Arcamone M, et al. Long-term results of gemcitabine plus oxaliplatin with and without rituximab as salvage treatment for transplant-ineligible patients with refractory/relapsing B-cell lymphoma. Cancer Chemother Pharmacol 2009;64:907-916. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19219604.

109. Mounier N, El Gnaoui T, Tilly H, et al. Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II Lymphoma Study Association trial. Haematologica 2013;98:1726-1731. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23753028.

110. Hoppe BS, Moskowitz CH, Filippa DA, et al. Involved-field radiotherapy before high-dose therapy and autologous stem-cell rescue in diffuse large-cell lymphoma: long-term disease control and toxicity. J Clin Oncol 2008;26:1858-1864. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18332466.

111. Weidmann E, Kim SZ, Rost A, et al. Bendamustine is effective in relapsed or refractory aggressive non-Hodgkin's lymphoma. Ann Oncol 2002;13:1285-1289. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12181253.

112. Wiernik PH, Lossos IS, Tuscano JM, et al. Lenalidomide monotherapy in relapsed or refractory aggressive non-Hodgkin's lymphoma. J Clin Oncol 2008;26:4952-4957. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18606983.

113. Hernandez-Ilizaliturri FJ, Deeb G, Zinzani PL, et al. Higher response to lenalidomide in relapsed/refractory diffuse large B-cell lymphoma in nongerminal center B-cell-like than in germinal center B-cell-like phenotype. Cancer 2011;117:5058-5066. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21495023.

114. Zinzani PL, Pellegrini C, Gandolfi L, et al. Combination of Lenalidomide and Rituximab in Elderly Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma: A Phase 2 Trial. Clin

Lymphoma Myeloma Leuk 2011;11:462-466. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/21859554.

115. Wang M, Fowler N, Wagner-Bartak N, et al. Oral Lenalidomide
with rituximab in relapsed or refractory diffuse large cell, follicular, and
transformed lymphoma: a phase II clinical trial. Leukemia
2013;27:1902-1909. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/23545991.

116. Zinzani PL, Vose JM, Czuczman MS, et al. Long-term follow-up of
lenalidomide in relapsed/refractory mantle cell lymphoma: subset
analysis of the NHL-003 study. Ann Oncol 2013;24:2892-2897.
Available at: http://www.ncbi.nlm.nih.gov/pubmed/24030098.

117. Gutierrez M, Chabner BA, Pearson D, et al. Role of a
doxorubicin-containing regimen in relapsed and resistant lymphomas:
an 8-year follow-up study of EPOCH. J Clin Oncol 2000;18:3633-3642.
Available at: http://www.ncbi.nlm.nih.gov/pubmed/11054436.

118. Jermann M, Jost LM, Taverna C, et al. Rituximab-EPOCH, an
effective salvage therapy for relapsed, refractory or transformed B-cell
lymphomas: results of a phase II study. Ann Oncol 2004;15:511-516.
Available at: http://www.ncbi.nlm.nih.gov/pubmed/14998858.

119. Gopal AK, Press OW, Shustov AR, et al. Efficacy and safety of
gemcitabine, carboplatin, dexamethasone, and rituximab in patients
with relapsed/refractory lymphoma: a prospective multi-center phase II
study by the Puget Sound Oncology Consortium. Leuk Lymphoma
2010;51:1523-1529. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/20578815.

120. Cazals-Hatem D, Lepage E, Brice P, et al. Primary mediastinal
large B-cell lymphoma. A clinicopathologic study of 141 cases
compared with 916 nonmediastinal large B-cell lymphomas, a GELA
("Groupe d'Etude des Lymphomes de l'Adulte") study. Am J Surg Pathol
1996;20:877-888. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/8669537.

121. Faris JE, LaCasce AS. Primary mediastinal large B-cell lymphoma.
Clin Adv Hematol Oncol 2009;7:125-133. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/19367254.

122. Rosenwald A, Wright G, Leroy K, et al. Molecular diagnosis of
primary mediastinal B cell lymphoma identifies a clinically favorable
subgroup of diffuse large B cell lymphoma related to Hodgkin
lymphoma. J Exp Med 2003;198:851-862. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/12975453.

123. Savage KJ, Monti S, Kutok JL, et al. The molecular signature of
mediastinal large B-cell lymphoma differs from that of other diffuse large
B-cell lymphomas and shares features with classical Hodgkin
lymphoma. Blood 2003;102:3871-3879. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/12933571.

124. Hamlin PA, Portlock CS, Straus DJ, et al. Primary mediastinal
large B-cell lymphoma: optimal therapy and prognostic factor analysis in
141 consecutive patients treated at Memorial Sloan Kettering from 1980
to 1999. Br J Haematol 2005;130:691-699. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/16115124.

125. Savage KJ, Al-Rajhi N, Voss N, et al. Favorable outcome of
primary mediastinal large B-cell lymphoma in a single institution: the
British Columbia experience. Ann Oncol 2006;17:123-130. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/16236753.

126. Todeschini G, Secchi S, Morra E, et al. Primary mediastinal large
B-cell lymphoma (PMLBCL): long-term results from a retrospective
multicentre Italian experience in 138 patients treated with CHOP or
MACOP-B/VACOP-B. Br J Cancer 2004;90:372-376. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/14735179.

127. Zinzani PL, Martelli M, Bertini M, et al. Induction chemotherapy
strategies for primary mediastinal large B-cell lymphoma with sclerosis:
a retrospective multinational study on 426 previously untreated patients.
Haematologica 2002;87:1258-1264. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/12495899.

128. De Sanctis V, Finolezzi E, Osti MF, et al. MACOP-B and involved-field radiotherapy is an effective and safe therapy for primary mediastinal large B cell lymphoma. Int J Radiat Oncol Biol Phys 2008;72:1154-1160. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18472357.

129. Mazzarotto R, Boso C, Vianello F, et al. Primary mediastinal large B-cell lymphoma: results of intensive chemotherapy regimens (MACOP-B/VACOP-B) plus involved field radiotherapy on 53 patients. A single institution experience. Int J Radiat Oncol Biol Phys 2007;68:823-829. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17379431.

130. Zinzani PL, Stefoni V, Finolezzi E, et al. Rituximab combined with MACOP-B or VACOP-B and radiation therapy in primary mediastinal large B-cell lymphoma: a retrospective study. Clin Lymphoma Myeloma 2009;9:381-385. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19858058.

131. Rieger M, Osterborg A, Pettengell R, et al. Primary mediastinal B-cell lymphoma treated with CHOP-like chemotherapy with or without rituximab: results of the Mabthera International Trial Group study. Ann Oncol 2011;22:664-670. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20724576.

132. Vassilakopoulos TP, Pangalis GA, Katsigiannis A, et al. Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone with or without radiotherapy in primary mediastinal large B-cell lymphoma: the emerging standard of care. Oncologist 2012;17:239-249. Available at:

133. Soumerai JD, Hellmann MD, Feng Y, et al. Treatment of primary mediastinal B-cell lymphoma with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone is associated with a high rate of primary refractory disease. Leuk Lymphoma 2014;55:538-543. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23734654.

134. Witzens-Harig M, Ho AD, Kuhnt E, et al. Primary Mediastinal B Cell Lymphoma Treated with CHOP-Like Chemotherapy with or without

Rituximab: 5-Year Results of the Mabthera International Trial Group (MInT) Study [abstract]. Blood 2012;120:Abstract 1612. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/120/21/1612.

135. Moskowitz C, Hamlin PA, Jr., Maragulia J, et al. Sequential dose-dense RCHOP followed by ICE consolidation (MSKCC protocol 01-142) without radiotherapy for patients with primary mediastinal large B-cell lymphoma. Blood 2010;116:420. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/420.

136. Quintanilla-Martinez L, de Jong D, de Mascarel A, et al. Gray zones around diffuse large B cell lymphoma. Conclusions based on the workshop of the XIV meeting of the European Association for Hematopathology and the Society of Hematopathology in Bordeaux, France. J Hematop 2009;2:211-236. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20309430.

137. Jaffe ES, Stein H, Swerdlow SH, et al. B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:267-268.

138. Hoeller S, Copie-Bergman C. Grey zone lymphomas: lymphomas with intermediate features. Adv Hematol 2012;2012:460801. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22548066.

139. Gualco G, Natkunam Y, Bacchi CE. The spectrum of B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma: a description of 10 cases. Mod Pathol 2012;25:661-674. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22222636.

140. Kanakry JA, Sehn LH, Feldman T, et al. Gray Zone Lymphoma (GZL) With Features Intermediate Between Classical Hodgkin Lymphoma (cHL) and Diffuse Large B-Cell Lymphoma (DLBCL): A Large Retrospective Multicenter Analysis Of Clinical Characteristics,

Treatment, Outcomes, and Prognosis In The Current Era. Blood 2013;122:847. Available at:
http://bloodjournal.hematologylibrary.org/content/122/21/847.abstract.

141. Traverse-Glehen A, Pittaluga S, Gaulard P, et al. Mediastinal gray zone lymphoma: the missing link between classic Hodgkin's lymphoma and mediastinal large B-cell lymphoma. Am J Surg Pathol 2005;29:1411-1421. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/16224207.

142. Eberle FC, Rodriguez-Canales J, Wei L, et al. Methylation profiling of mediastinal gray zone lymphoma reveals a distinctive signature with elements shared by classical Hodgkin's lymphoma and primary mediastinal large B-cell lymphoma. Haematologica 2011;96:558-566. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21454882.

143. Garcia JF, Mollejo M, Fraga M, et al. Large B-cell lymphoma with Hodgkin's features. Histopathology 2005;47:101-110. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/15982329.

144. Dunleavy K, Pittaluga S, Tay K, et al. Comparative Clinical and Biological Features of Primary Mediastinal B-Cell Lymphoma (PMBL) and Mediastinal Grey Zone Lymphoma (MGZL) [abstract]. Blood 2009;114:Abstract 106. Available at:
http://abstracts.hematologylibrary.org/cgi/content/abstract/114/22/106.

Burkitt Lymphoma

BL is a rare and aggressive B-cell tumor typically involving extranodal disease sites. In the WHO Classification, three clinical variants of BL are described: endemic, sporadic, and immunodeficiency-associated BL.[1] The endemic variant is the most common form of childhood malignancy occurring in equatorial Africa and the majority of cases are associated with Epstein-Barr virus (EBV) infection. Sporadic BL accounts for 1% to 2% of all adult lymphomas in the US and Western Europe, and can be associated with EBV infection in about 30% of cases.[1-3] Immunodeficiency-associated BL occurs mainly in patients infected with HIV, in some posttransplant patients and in individuals with congenital immunodeficiency. A recent analysis from the NCI SEER database reported improved survival outcomes in patients with BL diagnosed during the last decade (N=1922; year of diagnosis 2002–2008).[4] The 5-year survival estimate was 56% compared with 43% in patients diagnosed prior to 2002. Thus, durable remission may be possible in approximately 60% of patients with BL.

Diagnosis

Adequate immunophenotyping by flow cytometry analysis or immunohistochemistry (IHC) is needed to establish the diagnosis of BL. Flow cytometry analysis should include the following markers: CD5, CD10, CD19, CD20, CD45, TDT, and kappa/lambda. The IHC panel should include the following: CD3, CD10, CD20, CD45, TdT, Ki-67, BCL2, and BCL6. If immunophenotyping is performed using flow cytometry first, then IHC using selected markers (Ki-67 and BCL2) can supplement the findings from flow cytometry. EBV encoded RNA in situ hybridization (EBER ISH) may be useful to evaluate for EBV infection status in some cases.

The typical immunophenotype of BL is sIg+, CD10+, CD19+, CD20+, CD22+, TdT-, Ki67+ (>95%), BCL2-, BCL6+, and simple karyotype with *MYC* rearrangement. Translocations involving the *MYC* gene are detected in nearly all cases of BL. Most cases (80%) of classical BL are characterized by t(8;14) which results in the juxtaposition of *MYC* gene from chromosome 8 with the *IgH* region on chromosome14.[5] Other variants with *MYC* rearrangements [t(8;22) or t(2;8)] are less common. Some cases of DLBCL are also associated with an overexpression of *MYC*. Therefore, establishing the diagnosis of BL can be challenging using routine cytogenetic analysis. FISH using a break apart probe or long segment PCR are more reliable for the detection of t(8;14) and its variants.[6] Gene expression profiling also has been reported as an accurate, quantitative method for distinguishing BL from DLBCL.[7,8] However, this technique is not yet recommended for widespread clinical use. Cytogenetic analysis (with or without FISH) for detection of t(8;14) or variants should be performed in all cases with evaluation of *BCL2 or BCL6* gene rearrangements under certain circumstances.

The 2008 WHO lymphoma classification eliminates atypical BL. For cases without typical morphology or immunophenotype, a provisional category has been introduced, "B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL".[9,10] These are aggressive lymphomas with substantial heterogeneity in terms of morphology, immunophenotype, and genetic features.[9,11] Survival outcomes in patients with these lymphomas are poor, with a median survival of 9 months (and a 5-year survival rate of only 30%) reported in a retrospective analysis (N=39).[11] This group of lymphomas also includes cases that harbor both *MYC* and *BCL2* (and/or *BCL6*) translocations, the so-called "double-hit" lymphomas.[9,10] Such cases of "double-hit" lymphomas have a highly aggressive disease course with poor prognosis; case series have reported a median overall survival

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(OS) time of 4 to 6 months among patients with "double-hit" lymphomas.[12-14] The optimal management of patients with "double-hit" or "triple-hit" (involving *BCL6* translocation in addition to *MYC* and *BCL2* translocations)[12] lymphomas has not been identified. Further discussions concerning "double-hit" lymphomas are included under the section for DLBCL of the NCCN Guidelines for NHL.

Workup

The initial diagnostic workup includes a detailed physical examination (with special attention to the node bearing areas, liver and spleen) and CT scans of the chest, abdomen and pelvis. CT scan of the neck may be useful in certain cases. Adult patients with BL commonly present with bulky abdominal masses, B symptoms, and laboratory evidence of tumor lysis; in addition, bone marrow involvement (up to 70% of cases) and leptomeningeal CNS involvement (up to 40% of cases) may also be common findings at the time of diagnosis. Brain MRI may be useful under certain circumstances (e.g., if CNS involvement is suspected at time of diagnosis due to neurological signs or symptoms). PET or integrated PET-CT scans are not recommended for routine use, since it is unlikely that findings of PET or PET-CT would alter therapy for patients with newly diagnosed BL. If the treatment includes an anthracycline-containing regimen, cardiac evaluation with MUGA scan or echocardiogram is recommended, particularly for older patients.

Evaluations of bone marrow aspirates, biopsy, lumbar puncture and flow cytometry of cerebrospinal fluid are essential. In these highly aggressive lymphomas, as in DLBCLs, the serum LDH level has prognostic significance. These tumors exhibit a high degree of cellular proliferation, as determined by Ki-67 expression levels. Because BL is frequently associated with HIV infection, HIV serology should be part of the diagnostic workup for these diseases (for cases with positive HIV

serology, see recommendations for AIDS-related B-cell lymphoma in the NCCN Guidelines for NHL). In addition, testing for hepatitis B virus (HBV) should be performed, as chemoimmunotherapy regimens (often used in the treatment of BL) are associated with increased risks for HBV reactivation. Patients with serum LDH levels within normal ranges and with complete resection of abdominal lesions (or single extra-nodal mass < 10 cm) are generally considered to have low-risk disease; all other patients should be considered as high-risk cases.

Treatment Options

BL is curable in a significant subset of patients when treated with dose-intensive, multiagent chemotherapy regimens that also incorporates CNS prophylaxis. It is important to note that CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or similar regimens are not considered adequate therapy for the management of BL. In a recent population-based analysis of data from patients with BL (HIV-negative BL; N=258) from a Swedish/Danish registry, CHOP (or CHOP with etoposide) regimens resulted in a 2-year OS of only 39% compared with approximately 70% to 80% with more intensive multiagent chemotherapy regimens.[15] Thus, for patients with BL who can tolerate aggressive therapies, intensive multiagent chemotherapy may offer the best chance for durable disease control. About 60% to 90% of pediatric and young adult patients with BL achieve durable remission if treated appropriately.[16] However, the survival of older adults with BL appears to be less favorable, compared with younger patients.[17] Although the SEER database suggests that older adults (patients aged >40 years) represent about 60% of BL cases (with about 30% aged >60 years), this patient population is underrepresented in published clinical trials.[16,17] It is preferred that patients with BL receive treatment at centers with expertise in the management of this highly aggressive disease.

Most contemporary regimens used in adult patients have been developed from the pediatric protocols, and include intensive multiagent chemotherapy along with CNS prophylaxis with systemic and/or intrathecal chemotherapy. Tumor lysis syndrome is more common in patients with BL and should be managed as outlined under "Tumor Lysis Syndrome" in the Supportive Care section of the Guidelines and Discussion.

CODOX-M (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate), alternating with IVAC (ifosfamide, etoposide and high dose cytarabine) is a highly effective regimen developed by Magrath et al.[18] Both cycles included intrathecal chemotherapy (cytarabine or methotrexate) for CNS prophylaxis in addition to high-dose systemic cytarabine and methotrexate. In the updated results obtained with 4 cycles of CODOX-M/IVAC protocol given to previously untreated patients (n=55, BL or Burkitt-like lymphoma; n=11, DLBCL), the 1-year event-free survival (EFS) rate was 85%.[19]

In an international phase II study, Mead et al established the value of a modified CODOX-M/IVAC regimen in adults with BL (N=52 evaluable).[20] Low-risk patients (n=12) received modified CODOX-M (3 cycles) and high-risk patients (n=40) received modified CODOX-M and IVAC (alternating cycles for 4 cycles). In low-risk patients, 2-year EFS and OS rates were 83% and 81%, respectively, compared with 60% and 70%, respectively, for high- risk patients.[20] The efficacy of the modified CODOX-M/IVAC regimen in high-risk BL (n=42) was confirmed in a subsequent trial, which reported 2-year progression-free survival (PFS) and OS rates of 62% and 64%, respectively.[21] Modified CODOX-M regimen with or without alternating IVAC was also effective and well tolerated in older patients with BL or Burkitt-like lymphoma (N=14)[22] and in patients with HIV-associated BL (n=8).[23]

More recently, the addition of the anti-CD20 monoclonal antibody rituximab has been investigated in combination with CODOX-M/IVAC, given that most cases of BL are CD20-positive. In a small study that evaluated CODOX-M/IVAC with or without rituximab in patients with BL or B-cell lymphoma unclassifiable (N=15), the 5-year PFS and OS rates were 87% for both outcome measures.[24] In a larger retrospective study in patients with BL (N=80) treated with CODOX-M/IVAC with or without rituximab, the 3-year EFS and OS rates with rituximab were 74% and 77%, respectively; the 3-year EFS and OS rates without the addition of rituximab was 61% and 66%, respectively.[25] Although a trend for improvement in outcomes with the addition of rituximab was observed, the differences were not statistically significant. In another recent retrospective study that evaluated outcomes with different regimens in patients with BL (N=258), 2-year OS with CODOX-M/IVAC (with or without rituximab) was 69%.[15]

The hyper-CVAD regimen (hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with methotrexate and cytarabine, including intrathecal methotrexate) developed by the MD Anderson Cancer Center, has also been evaluated in patients with Burkitt-lymphoma/leukemia (N=26).[26] With this regimen, complete remission (CR) was achieved in 81% of patients and the 3-year OS rate was 49%; OS rate was higher among patients aged 60 years or younger (77% vs. 17% for patients older than 60 years).[26] In a phase II trial in HIV-negative patients with newly diagnosed BL or B-ALL (N=31), the addition of rituximab to the hyper-CVAD regimen (R-hyper-CVAD) induced CR in 86% of patients; the 3-year EFS and disease-free survival rates were 80% and 88%, respectively.[27] The 3-year OS rates were similar among the elderly and younger patients (89% vs. 88%).[27] In the updated report (n = 57; 30 patients non-HIV BL and 27 patients with B-ALL) , with a median follow up of 62 months, the 5-year OS rate with R-hyper-CVAD was

74%; the corresponding OS rates in patients younger than 60 years and those older than 60 years were 72% and 70%, respectively.[28] In a historical comparison with patients treated with hyper-CVAD alone (corresponding 5-year OS rates 50%, 70%, and 19%, respectively), outcomes were superior with the R-hyper-CVAD regimen. The results of this study showed that the addition of rituximab to hyper-CVAD improved long-term outcomes in patients with BL or B-ALL, particularly in the older patient subgroup. In a recent retrospective study that evaluated outcomes with different regimens in patients with BL (N=258), the 2-year OS rate was one of the highest with the use of hyper-CVAD (with or without rituximab), at 83%.[15]

The CALGB 9251 study evaluated the efficacy of intensive multiagent chemotherapy with and without cranial radiation for central nervous system (CNS) prophylaxis in adult patients with Burkitt leukemia or lymphoma.[29] Given the severe neurotoxicity, the protocol was amended after the first 52 of 92 patients were enrolled. The 3-year EFS rate was 52% in the cohort of patients who received intensive CNS prophylaxis (cranial RT and 12 doses of triple intrathecal chemotherapy) compared to 45% in those who received only 6 doses of intrathecal chemotherapy and cranial irradiation (the latter for high-risk patients only).[29] The subsequent CALGB 10002 study investigated the addition of rituximab and growth factor support to the above CALGB 9251 regimen, and without the use of prophylactic CNS irradiation.[30] Among patients with previously untreated BL or Burkitt-like lymphoma/leukemia (N=103 evaluable), 82% achieved a CR and 7% had a partial remission (PR). The 4-year EFS and OS rates were 74% and 78%, respectively; as would be expected, these survival outcomes were more favorable among the subgroup of patients with low-risk IPI scores (4-year EFS and OS rates 86% and 90%, respectively) compared with those with high-risk IPI scores (55% and 55%, respectively).

A recent prospective study (30 patients with perviously untreated BL) evaluated the standard dose-adjusted EPOCH with rituximab (DA-EPOCH-R) in HIV-negative patients (n = 19) and a lower-dose short-course regimen with a double dose of rituximab (SC-EPOCH-RR) in HIV-positive patients (n =11).[31] At a median follow up of 86 months, the FFP and OS rates with DA-EPOCH-R were 95% and 100%, respectively. The highly favorable outcomes seen in this study may reflect the inclusion of more low-risk patients compared to other studies, with approximately 53% of all patients (37% in the DA-EPOCH-R group) presenting with normal LDH levels.

A prospective multicenter study from the German study group evaluated the efficacy and safety of a new short-intensive regimen combined with rituximab in patients with CD20-positive BL and Burkitt leukemia (N=363).[32] The regimen comprised multiagent chemotherapy with high-dose methotrexate, high-dose cytarabine, cyclophosphamide, etoposide, ifosfamide and corticosteroids, combined with rituximab. Patients also received triple intrathecal therapy with methotrexate, cytarabine, and dexamethasone. Among the patients with BL (n=229), the CR rate with this regimen was 91%; at a median follow up of more than 7 years, the PFS and OS rates in the BL subgroup were 83% and 88%, respectively.[32] Frequent grade 3 or 4 toxicities among patients with BL included neutropenia (64%), mucositis (31%), and infections (23%). These outcomes appear highly promising, with a manageable toxicity profile.[32]

Several studies have evaluated the role of hematopoietic stem cell transplantation (HSCT) in patients with BL. The Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) demonstrated the feasibility of intensive high-dose induction chemotherapy (prednisone, cyclophosphamide, doxorubicin, etoposide and mitoxantrone, without high-dose methotrexate or high-dose cytarabine) followed by

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consolidation with BEAM and autologous HSCT in untreated adults with BL, Burkitt-like lymphoma, or B-ALL.[33] Among the patients with BL/Burkitt-like lymphoma (n=27), CR was achieved in 81% of patients with a PR in 11%; the 5-year EFS and OS rates were 73% and 81%, respectively.[33] In a recent analysis of outcomes with HSCT (autologous or allogeneic transplant) in patients with BL from the CIBMTR database (N=241), the 5-year PFS and OS rates with autologous HSCT at first remission were 78% and 83%, respectively.[34] These outcomes with autologous HSCT were similar to findings from the above HOVON study, and appeared to compare favorably to the 5-year PFS and OS rates with allogeneic HSCT in first remission, which were 50% and 53%, respectively. Not surprisingly, patients who underwent HSCT with less than a first remission had poorer outcomes regardless of transplant type. The 5-year PFS and OS rates with autologous HSCT in those without a first remission were 27% and 31%, respectively; the corresponding rates with allogeneic HSCT without first remission were only 19% and 20%, respectively. For patients in a second remission, autologous HSCT resulted in a 5-year PFS of 44%.[34] An earlier retrospective analysis from the CIBMTR database in patients with relapsed or refractory BL (children and adolescents age ≤ 18 years; n=41) showed similar 5-year EFS outcomes between autologous and allogeneic HSCT (27% vs. 31%).[35] As would be expected, EFS rates were lower among patients who were not in CR at the time of transplant.

The management of patients with B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL, as well as those patients with "double-hit" B-cell lymphoma has not been well studied. Patients with "double-hit" lymphomas have very poor prognosis, with a median OS of only 4 to 6 months with chemotherapy combinations (e.g., CHOP, CODOX-M/IVAC, hyper-CVAD, EPOCH), with or without the incorporation of rituximab.[12,14,21,36] Therefore, these patients are

best managed in the context of clinical trials evaluating novel targeted agents.

NCCN Recommendations

Induction Therapy
Participation in clinical trials is recommended for all patients. As mentioned earlier, CHOP or CHOP-like therapy is not adequate for the treatment of BL. The NCCN Guidelines panel recommends the following regimens for induction therapy, which should also include adequate CNS prophylaxis with systemic and/or intrathecal chemotherapy with methotrexate and/or cytarabine:

- CALGB 10002 regimen
- CODOX-M/IVAC (original or modified) with or without addition of rituximab
- Dose-adjusted EPOCH with rituximab (DA-EPOCH-R)
- Hyper-CVAD with rituximab (R-hyper-CVAD)

Patients with CR to induction therapy should be followed up every 2 to 3 months for 1 year then every 3 months for the next 1 year and then every 6 months thereafter. Disease relapse after 2 years is rare following CR to induction therapy, and follow up should be individualized according to patient characteristics. Consolidation therapy in the context of a clinical trial may be considered for high-risk patients with CR to induction therapy. Patients with less than CR to induction therapy should be treated in the context of a clinical trial. In the absence of suitable clinical trials palliative RT may be considered appropriate.

Relapsed or Refractory Disease
Patients with relapsed or refractory disease should be treated in the context of a clinical trial. Second-line chemotherapy with rituximab-containing regimens followed by high-dose therapy and

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autologous HSCT or allogeneic HSCT (if donor available) may be considered in selected patients with a reasonable remission duration following induction therapy. However, the treatment options remain undefined for patients who relapse after first-line therapy.

The guidelines have included DA-EPOCH-R, IVAC combined with rituximab (R-IVAC). R-GDP (gemcitabine, dexamethasone, cisplatin, combined with rituximab), R-ICE (ifosfamide, carboplatin, etoposide, combined with rituximab), and high-dose cytarabine as options for second-line therapy. However, it should be noted that these suggestions are based on very limited, retrospective studies with only a few patients. For instance, the R-ICE regimen was evaluated in a small group of pediatric patients with relapsed BL and B-ALL (n=14), which resulted in CR in 29% and PR in 36% of patients.[37]

The best options for patients requiring second-line therapy for relapsed/refractory disease are investigational treatments in the context of clinical trials. In the absence of suitable clinical trials or for patients unlikely to benefit from additional intensive multiagent chemotherapy regimens, best supportive care should be considered appropriate.

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References

1. Leoncini L, Raphael M, Stein H, et al. Burkitt lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:262-264.

2. Blum KA, Lozanski G, Byrd JC. Adult Burkitt leukemia and lymphoma. Blood 2004;104:3009-3020. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15265787.

3. Aldoss I, Weisenburger D, Fu K, et al. Adult Burkitt lymphoma: advances in diagnosis and treatment. Oncology (Williston Park) 2008;22:1508-1517. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19133605.

4. Costa LJ, Xavier AC, Wahlquist AE, Hill EG. Trends in survival of patients with Burkitt lymphoma/leukemia in the USA: an analysis of 3691 cases. Blood 2013;121:4861-4866. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23641015.

5. Ferry JA. Burkitt's lymphoma: clinicopathologic features and differential diagnosis. Oncologist 2006;11:375-383. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16614233.

6. Burmeister T, Schwartz S, Horst HA, et al. Molecular heterogeneity of sporadic adult Burkitt-type leukemia/lymphoma as revealed by PCR and cytogenetics: correlation with morphology, immunology and clinical features. Leukemia 2005;19:1391-1398. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15973450.

7. Dave SS, Fu K, Wright GW, et al. Molecular diagnosis of Burkitt's lymphoma. N Engl J Med 2006;354:2431-2442. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16760443.

8. Hummel MI, Bentink S, Berger H, et al. A biologic definition of Burkitt's lymphoma from transcriptional and genomic profiling. N Engl J

Med 2006;354:2419-2430. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16760442.

9. Kluin PM, Raphael M, Harris NL, et al. B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:265-266.

10. Hasserjian RP, Ott G, Elenitoba-Johnson KS, et al. Commentary on the WHO classification of tumors of lymphoid tissues (2008): "Gray zone" lymphomas overlapping with Burkitt lymphoma or classical Hodgkin lymphoma. J Hematop 2009. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19669187.

11. Perry AM, Crockett D, Dave BJ, et al. B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and burkitt lymphoma: study of 39 cases. Br J Haematol 2013. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23600716.

12. Tomita N, Tokunaka M, Nakamura N, et al. Clinicopathological features of lymphoma/leukemia patients carrying both BCL2 and MYC translocations. Haematologica 2009;94:935-943. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19535347.

13. Johnson NA, Savage KJ, Ludkovski O, et al. Lymphomas with concurrent BCL2 and MYC translocations: the critical factors associated with survival. Blood 2009;114:2273-2279. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19597184.

14. Snuderl M, Kolman OK, Chen YB, et al. B-cell lymphomas with concurrent IGH-BCL2 and MYC rearrangements are aggressive neoplasms with clinical and pathologic features distinct from Burkitt lymphoma and diffuse large B-cell lymphoma. Am J Surg Pathol 2010;34:327-340. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20118770.

15. Wasterlid T, Brown PN, Hagberg O, et al. Impact of chemotherapy regimen and rituximab in adult Burkitt lymphoma: a retrospective population-based study from the Nordic Lymphoma Group. Ann Oncol 2013;24:1879-1886. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23446093.

16. Perkins AS, Friedberg JW. Burkitt lymphoma in adults. Hematology Am Soc Hematol Educ Program 2008:341-348. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19074108.

17. Kelly JL, Toothaker SR, Ciminello L, et al. Outcomes of patients with Burkitt lymphoma older than age 40 treated with intensive chemotherapeutic regimens. Clin Lymphoma Myeloma 2009;9:307-310. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19717381.

18. Magrath I, Adde M, Shad A, et al. Adults and children with small non-cleaved-cell lymphoma have a similar excellent outcome when treated with the same chemotherapy regimen. J Clin Oncol 1996;14:925-934. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8622041.

19. Adde M, Shad A, Venzon D, et al. Additional chemotherapy agents improve treatment outcome for children and adults with advanced B-cell lymphomas. Semin Oncol 1998;25:33-39; discussion 45-48. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9578060.

20. Mead GM, Sydes MR, Walewski J, et al. An international evaluation of CODOX-M and CODOX-M alternating with IVAC in adult Burkitt's lymphoma: results of United Kingdom Lymphoma Group LY06 study. Ann Oncol 2002;13:1264-1274. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12181251.

21. Mead GM, Barrans SL, Qian W, et al. A prospective clinicopathologic study of dose-modified CODOX-M/IVAC in patients with sporadic Burkitt lymphoma defined using cytogenetic and immunophenotypic criteria (MRC/NCRI LY10 trial). Blood 2008;112:2248-2260. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18612102.

22. Lacasce A, Howard O, Lib S, et al. Modified Magrath regimens for adults with Burkitt and Burkitt-like lymphomas: preserved efficacy with decreased toxicity. Leuk Lymphoma 2004;45:761-767. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15160953.

23. Wang ES, Straus DJ, Teruya-Feldstein J, et al. Intensive chemotherapy with cyclophosphamide, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine (CODOX-M/IVAC) for human immunodeficiency virus-associated Burkitt lymphoma. Cancer 2003;98:1196-1205. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12973843.

24. Maruyama D, Watanabe T, Maeshima AM, et al. Modified cyclophosphamide, vincristine, doxorubicin, and methotrexate (CODOX-M)/ifosfamide, etoposide, and cytarabine (IVAC) therapy with or without rituximab in Japanese adult patients with Burkitt lymphoma (BL) and B cell lymphoma, unclassifiable, with features intermediate between diffuse large B cell lymphoma and BL. Int J Hematol 2010;92:732-743. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21120644.

25. Barnes JA, Lacasce AS, Feng Y, et al. Evaluation of the addition of rituximab to CODOX-M/IVAC for Burkitt's lymphoma: a retrospective analysis. Ann Oncol 2011;22:1859-1864. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21339382.

26. Thomas DA, Cortes J, O'Brien S, et al. Hyper-CVAD program in Burkitt's-type adult acute lymphoblastic leukemia. J Clin Oncol 1999;17:2461-2470. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10561310.

27. Thomas DA, Faderl S, O'Brien S, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer 2006;106:1569-1580. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16502413.

28. Thomas DA, Kantarjian HM, Faderl S, et al. Hyper-CVAD and Rituximab for De Novo Burkitt Lymphoma/Leukemia [abstract]. Blood 2011;118:Abstract 2698. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;118/21/2698.

29. Rizzieri DA, Johnson JL, Niedzwiecki D, et al. Intensive chemotherapy with and without cranial radiation for Burkitt leukemia and lymphoma: final results of Cancer and Leukemia Group B Study 9251. Cancer 2004;100:1438-1448. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15042678.

30. Rizzieri DA, Johnson JL, Byrd JC, et al. Improved efficacy using rituximab and brief duration, high intensity chemotherapy with filgrastim support for Burkitt or aggressive lymphomas: cancer and Leukemia Group B study 10 002. Br J Haematol 2014;165:102-111. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24428673.

31. Dunleavy K, Pittaluga S, Shovlin M, et al. Low-intensity therapy in adults with Burkitt's lymphoma. N Engl J Med 2013;369:1915-1925. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24224624.

32. Hoelzer D, Walewski J, Dohner H, et al. Substantially Improved Outcome of Adult Burkitt Non-Hodgkin Lymphoma and Leukemia Patients with Rituximab and a Short-Intensive Chemotherapy; Report of a Large Prospective Multicenter Trial [abstract]. Blood 2012;120:Abstract 667. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/120/21/667.

33. van Imhoff GW, van der Holt B, MacKenzie MA, et al. Short intensive sequential therapy followed by autologous stem cell transplantation in adult Burkitt, Burkitt-like and lymphoblastic lymphoma. Leukemia 2005;19:945-952. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15800666.

34. Maramattom LV, Hari PN, Burns LJ, et al. Autologous and allogeneic transplantation for burkitt lymphoma outcomes and changes in utilization: a report from the center for international blood and marrow transplant research. Biol Blood Marrow Transplant 2013;19:173-179. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23200705.

35. Gross TG, Hale GA, He W, et al. Hematopoietic stem cell transplantation for refractory or recurrent non-Hodgkin lymphoma in children and adolescents. Biol Blood Marrow Transplant 2010;16:223-230. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19800015.

36. Le Gouill S, Talmant P, Touzeau C, et al. The clinical presentation and prognosis of diffuse large B-cell lymphoma with t(14;18) and 8q24/c-MYC rearrangement. Haematologica 2007;92:1335-1342. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18024371.

37. Griffin TC, Weitzman S, Weinstein H, et al. A study of rituximab and ifosfamide, carboplatin, and etoposide chemotherapy in children with recurrent/refractory B-cell (CD20+) non-Hodgkin lymphoma and mature B-cell acute lymphoblastic leukemia: a report from the Children's Oncology Group. Pediatr Blood Cancer 2009;52:177-181. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18816698.

Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

CLL/SLL comprises approximately 7% of newly diagnosed cases of NHL.[1] CLL remains the most common adult leukemia in Western countries but is considered rare in regions such as East Asia. In the U.S. alone, 15,680 new cases of CLL and 4,580 deaths are estimated in 2013.[2] Morphologically, the leukemic cells appear as small, mature lymphocytes that may be found admixed with larger or atypical cells, cleaved cells, or prolymphocytes.[3] CLL is characterized by progressive accumulation of these leukemic cells in the peripheral blood, bone marrow, and lymphoid tissues. CLL and SLL are different manifestations of the same disease and are managed in much the same way.[4] The major difference is that in CLL, a significant number of the abnormal lymphocytes are also found in the bone marrow and blood, while in SLL the abnormal lymphocytes are predominantly found in the lymph nodes.

Diagnosis

The diagnosis of CLL requires the presence of at least 5000 clonal B-cells/mcL in the peripheral blood.[3] The presence of fewer B-cells in the absence of lymphadenopathy or other clinical features characteristic of a lymphoproliferative disorder is defined as monoclonal B-lymphocytosis (MBL). MBL is a relatively recent diagnostic category describing individuals who present with an abnormal B-cell population but do not meet the diagnostic criteria for CLL.[5] Most cases of MBL have the immunophenotype of CLL (see below). Favorable molecular lesions, mutated immunoglobulin heavy-chain variable region gene (*IGHV*) and chromosomal abnormality del(13q), are commonly seen in

patients with MBL.[6] The estimated rate of progression of MBL to CLL requiring treatment was 1.1% per year. To distinguish MBL from SLL, evaluation with CT scan is essential. The CLL/SLL guideline now includes an initial stratification between CLL/SLL and MBL (absolute B-lymphocyte count of less than 5000/mcL, lymph nodes less than 1.5 cm, no anemia or thrombocytopenia). Observation is recommended for all patients diagnosed with MBL. The diagnosis of SLL requires the presence of no more than 5000 B-lymphocytes/mcL in the peripheral blood, and the presence of lymphadenopathy and/or splenomegaly.[3] B-cells with a CLL/SLL phenotype may be found in samples from patients with reactive lymph nodes; however, a diagnosis of SLL should only be made when effacement of the lymph node architecture is observed in biopsy samples.

Adequate immunophenotyping is required to establish the diagnosis of CLL/SLL. Flow cytometry of peripheral blood is adequate for the diagnosis of CLL, and a biopsy is generally not required. Cell surface markers for flow cytometric studies should include kappa/lambda, CD19, CD20, CD5, CD23 and CD10. If flow cytometry is used to establish a diagnosis, flow evaluation for cyclin D1 or fluorescence in situ hybridization (FISH) analysis for t(11;14) should also be included. Paraffin-section immunohistochemistry (IHC) on excisional or incisional lymph node biopsy materials can be performed if a diagnosis is not established by flow cytometry. Recommended panel for IHC include CD3, CD5, CD10, CD20, CD23 and cyclin D1. These can be useful, particularly for diagnosing CLL/ SLL type without circulating leukemic cells. A diagnosis of SLL should ideally be confirmed by evaluation of lymph node biopsy.

The typical immunophenotype for CLL/SLL is CD5+, CD10-, CD19+, and CD20 dim, surface immunoglobulin dim, CD23+, CD43 +/-, and cyclin D1-. Distinguishing CLL/SLL from mantle cell lymphoma (MCL) is

essential, as they are both CD5+ B-cell tumors. Though CD23 is often helpful, absence of cyclin D1 expression is critical in this differentiation of tumor types. Stimulated cytogenetics or FISH analysis for t(11;14) can help to distinguish MCL from CLL, and should be performed if flow cytometry alone is used to evaluate immunophenotype. FISH for detection of del(11q), del(13q), trisomy 12 and del(17p), and molecular genetic analysis (by PCR or sequencing) to detect *IGHV* mutation status and *TP53* mutations can provide useful prognostic information and may guide selection of therapy (see Discussion section below for 'Prognostic Factors'). Though FISH is optional for patients with Rai low risk disease where observation would be recommended, it should be evaluated at the time therapy is considered. Cytogenetic abnormalities can evolve over time; therefore, re-evaluation of FISH is necessary to direct treatment options in patients with indications for treatment. CD38 and/or zeta-associated protein 70 (ZAP-70) expressions can be determined using immunohistochemistry or flow cytometry. However, evaluation of ZAP-70 expression (especially by flow cytometry) can be challenging and is not recommended outside the context of clinical trials.

Conventional metaphase cytogenetics is difficult in CLL as a result of the very low proliferative activity of the leukemic cells in vitro. Therefore, interphase cytogenetic analysis with FISH has been the standard method to detect chromosomal abnormalities that may have prognostic significance. However, FISH can only detect abnormalities specific to the probes utilized. Cytokine or CpG oligonucleotide stimulation has been utilized to promote efficient metaphase analysis.[7] Recent studies have demonstrated that stimulation with CpG oligonucleotide and interleukin-2 is more effective than that with 12-O-tetradecanoyl-phorbol-13-acetate (TPA) for the detection of chromosomal abnormalities in CLL.[8,9] A prospective study conducted

by CLL Research Consortium confirmed that abnormal clones in CLL are more readily detected with CpG oligonucleotide stimulation than with traditional B-cell mitogens; moreover, the clonal abnormalities revealed by CpG stimulated metaphase cytogenetics are consistent with that detected by interphase FISH and are reproducible among different cytogenetic laboratories.[10] However, the use of CpG stimulation for CLL cytogenetics is not yet universally available.

Prognostic Factors
During the past decade, numerous factors have been identified and evaluated in patients with CLL, which may provide useful prognostic information beyond clinical staging (see Discussion section below for 'Staging'). These factors include serum markers such as thymidine kinase and beta-2 microglobulin, genetic markers including *IGHV* mutational status and cytogenetic abnormalities detected by FISH (e.g., del(13q), del(11q), del(17p)), CD38 expression, and ZAP-70 expression.[11-22]

IGHV mutational status is an important predictor of survival outcomes in CLL; unmutated *IGHV* (≥98% homology with germline gene sequence) is associated with poor prognosis and significantly decreased survival compared with cases with mutated *IGHV*, irrespective of the stage of the disease.[12,17] In addition, *IGHV* rearrangements involving the *VH3-21* gene is associated with poor outcomes regardless of the mutation status (as defined by percent homology with germline sequence).[23] Unmutated *IGHV* or the use of *VH3-21* has been shown to be independent predictors of treatment-free intervals and/or survival outcomes, even when high-risk genomic abnormalities (see Discussion below on cytogenetic abnormalities detected by FISH) were included in the multivariable regression models.[24-27]

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Discussion

Expression of CD38 (≥7% of B lymphocytes)[12,13,19,25,26,28] and/or ZAP-70 (≥20% of B lymphocytes)[11,20-22,29] are also associated with shorter progression-free survival (PFS) and overall survival (OS) outcomes. Both CD38 and ZAP-70 positivity correlate with unmutated *IGHV*, and have been suggested as potential surrogate markers for *IGHV* mutational status.[11,12,22] However, discordant results between CD38 positivity and *IGHV* mutational status have been observed in up to 28% of patients in one study; moreover, CD38 expression levels may vary over the course of the disease.[18] Similarly, discordant results between ZAP-70 positivity and *IGHV* mutational status have been reported in 20-25% of cases.[21,26] In addition, it has been suggested that ZAP-70 positivity may be a stronger predictor of outcomes (e.g., time to first treatment) than *IGHV* mutational status or CD38 levels.[21,29,30] It should be noted, however, that standardization and reproducibility of ZAP-70 flow cytometry methods across laboratories remains a challenge.

Elevated levels of serum beta-2 microglobulin have been shown to be a strong independent prognostic indicator for treatment-free intervals, response to treatment, and OS, including in patients treated with first-line chemoimmunotherapy regimens.[31-33] One of the advantages of beta-2 microglobulin is that it is readily measured by standard laboratory evaluations of blood samples. Wierda et al developed a prognostic nomogram using clinical and laboratory parameters that are available in the routine clinical practice setting (age, beta-2 microglobulin, absolute lymphocyte count, sex, Rai stage, and number of involved lymph nodes); the nomogram was developed to estimate the median survival time, as well as the probability of 5-year and 10-year survival. In addition, based on the sum of points assigned to the six parameters used for the nomogram, a more simplified prognostic index was developed to help stratify untreated patients with CLL into

three different risk groups (low, intermediate and high).[34] The estimated median survival was not reached for the low-risk group. The median survival times for intermediate- and high-risk groups were 10 and 5 years, respectively. The 5-year survival rates were 97% for low-risk, 80% for intermediate-risk, and 55% for high-risk groups; the 10-year survival rates were 80%, 52%, and 26%, respectively.[34] It should be noted that sufficient data were not available for recently identified prognostic factors (e.g., *IGHV* mutational status, ZAP-70, cytogenetic abnormalities detected by FISH) to be incorporated into this version of the prognostic model (see Discussion section that follows for a recent prognostic nomogram that includes newer biological factors in addition to clinical and laboratory parameters, for estimating time to first treatment). Nevertheless, several studies have independently confirmed the utility of this prognostic index in estimating both survival probability and time to first treatment in previously untreated patients with CLL, including in patients with early-stage (Rai stage 0) disease.[35,36]

Cytogenetic abnormalities that can be detected by FISH are present in about 80% of patients with previously untreated CLL. The most common abnormality is del(13q) (55%) followed by del(11q) (18%), trisomy 12 (16%), del(17p) (7%), and del(6q) (7%).[14] Del(13q) is associated with a favorable prognosis and the longest median survival (133 months). Del(11q) is often associated with extensive lymphadenopathy, disease progression and shorter median survival (79 months).[14,37] Among patients with del(11q), those with a complete loss of *ATM* function might have impaired response to irradiation or cytotoxic drugs, resulting in poor clinical outcome.[38] Recent studies showed that previously untreated patients with del(11q) respond well to combination therapy with fludarabine and cyclophosphamide (FC), suggesting that the addition of an alkylating agent to fludarabine may

help to overcome the adverse prognostic significance of del(11q) in patients with CLL.[26,39] Del(17p), which frequently results in abnormalities of a key tumor suppressor gene *TP53*, is associated with worst outcomes, with short treatment free intervals, short median survival (32 months), and poor response to chemotherapy.[14] The phase III randomized CLL8 study of the German CLL Study Group (first-line FC vs. rituximab combined with FC [FCR]) showed that both del(17p) and unmutated *IGHV* were significant independent predictors of poor survival outcomes, irrespective of the treatment arm.[40] Although FCR was associated with significantly improved PFS among patients with del(17p), the 3-year PFS rate was only 18% in this subgroup. In addition, OS outcomes in patients with del(17p) were similar between FCR and FC arms (3-year OS 38% vs. 37%, respectively).[40] The prognostic importance of del(17p) may be dependent on the proportion of malignant cells with this abnormality. In the UK CLL4 trial (comparing first-line therapy with chlorambucil vs. fludarabine vs. FC), similar outcomes were observed between patient subgroups with 5% to 10% of cells with *TP53* deletion (i.e., del(17p13.1)) and the subgroup without *TP53* deletion (deletion in <5% of cells); patients with 10% to 20% *TP53* deletion had outcomes similar to patients with more than 20% *TP53* deletion.[26,41] Patients with 10% or more cells with *TP53* deletion had a poor outcome with 29% response rate (6% complete or nodular partial response) and a median survival of <6 months.[26] The finding that del(17p) is more frequently observed in treated patients than in untreated patients suggests that treatment-driven clonal selection may occurs during therapy. Indeed, acquisition and/or expansion of CLL clones with del(17p) have been observed during the course of treatment.[42] Recently, a prognostic nomogram for estimating time to first treatment was developed based on a multivariable model that included both traditional clinical and laboratory parameters as well as newer

prognostic factors (such as FISH cytogenetics, *IGHV* mutational status, and ZAP-70 expression levels).[43] The following factors were identified as independent predictors of shorter time to first treatment, and were included in a weighted model to estimate the probability of treatment (at 2- and 4-years) and time to first treatment: increased size of cervical lymph nodes, 3 involved nodal sites, del(17p) or del(11q), unmutated *IGHV* status, and elevated serum LDH levels.[43] This nomogram may help to identify newly diagnosed patients at high risk for disease progression who may require earlier intervention.

Abnormalities of *TP53* can be observed in the absence of del(17p).[44,45] Studies with fludarabine-based regimens have identified *TP53* mutations as an independent predictor of decreased survival and resistance to chemotherapy.[44-47] The resistance to chemotherapy has been attributed to the presence of mutation in the remaining *TP53* allele.[48] Thus, the presence of *TP53* mutation predicts for poor survival outcomes independent of 17p chromosome status.[44,45] In an analysis from the CLL8 study, mutation in *TP53* was associated with significantly decreased PFS and OS outcomes regardless of treatment with FCR or FC.[45]

The impact of these prognostic factors on the clinical outcome of patients has been examined in large prospective randomized studies. In the long-term follow up from the CALGB 9712 study (first-line therapy with concurrent vs. sequential fludarabine and rituximab), unmutated *IGHV* was a significant independent predictor for decreased PFS and OS, while poor-risk cytogenetic abnormalities (i.e., del(17p) or del(11q)) remained an independent predictor for decreased survival.[49] In the UK CLL4 trial, *TP53* loss was found to be the strongest predictor of poor outcomes.[26,46] Among the subgroup of patients without *TP53* loss, unmutated *IGHV* (or *VH3-21* usage) and elevated beta-2 microglobulin (>4 mg/L) were significant independent

predictors for both PFS and OS outcomes.[26] In addition, del(11q) and treatment allocation were independent predictors for PFS and age was an independent predictor for OS. In the German CLL8 trial (first-line FC vs. FCR), *TP53* mutations, del(17p), unmutated *IGHV*, and treatment arm were significant independent prognostic factors for both PFS and OS outcomes.[45]

During the last few years, other recurrent genetic lesions with prognostic implications in CLL have been identified. Examples of such lesions include mutations in *NOTCH1*, *SF3B1* and/or *BIRC3* genes. Mutations in *NOTCH1* (a proto-oncogene) occur in about 5% to 10% of patients with newly diagnosed CLL, and has been associated with decreased treatment-free survival and OS.[50-52] Although the presence of *NOTCH1* mutations tended to be mutually exclusive with *TP53* abnormalities, the survival outcomes were similarly poor.[51] Mutations in *SF3B1* (encoding a splicing factor) occur in about 5% to 15% of patients, and has also been associated with decreased PFS and/or OS in both previously untreated and refractory CLL.[50,52-54] Several studies suggest that *SF3B1* mutations may be less frequent among newly diagnosed patients (5–6%) than among those with fludarabine-refractory disease (17%),[54-56] although an analysis from the UK CLL4 trial reported a high incidence of this mutation (17%) in previously untreated patients.[50] Mutations in *SF3B1* appear to be associated with del(11q) cases.[52,56] Recent analysis from the aforementioned UK CLL4 trial (evaluation of first-line chlorambucil vs. fludarabine vs. FC combination) showed that both *NOTCH1* and *SF3B1* mutations were associated with decreased OS, and both retained independent prognostic significance for survival outcomes based on multivariable analysis.[50] Contrastingly, in the German CLL2H study of alemtuzumab in fludarabine-refractory CLL, *NOTCH1* mutations were associated with longer PFS compared with wild-type cases, and *SF3B1* mutations

were not predictive of outcomes (response rates, PFS or OS); in multivariable analysis, *NOTCH1* mutation was found to be an independent factor for favorable PFS in this patient population.[56] In a recent study based on data from a large multicenter series of newly diagnosed patients with CLL, *NOTCH1* mutations were found to be associated with increased risks for clonally related Richter's syndrome.[55] For cases of CLL with *NOTCH1* mutations at diagnosis, the cumulative probability of developing Richter's syndrome was significantly higher compared with cases without the mutation (45% vs. 5% at 15 years; *P*<0.001). For cases with *SF3B1* mutations at diagnosis, no association was found with the development of Richter's syndrome.[55] Collectively, the above studies suggest that the prognostic significance of these mutations may vary depending on the patient population, treatment regimens, and clinical outcomes being evaluated. Mutations in the *BIRC3* gene (encoding a negative regulator of signalling for the transcription factor nuclear factor kappa B [NF-κB]) have been reported in approximately 5% of patients with newly diagnosed CLL; in cases of fludarabine-refractory CLL, *BIRC3* mutations occurred at a higher frequency (approximately 25%).[57] Recent studies suggested that mutations in *BIRC3* were associated with refractoriness to chemotherapy, with a poor prognosis similar to cases with *TP53* abnormalities.[57,58]

Although these prognostic factors can be informative in the management of patients with CLL, treatment initiation should not be based on the presence of such factors. Moreover, in the general clinical practice setting, prognostic factors should not determine treatment choices, with the exception of cases with del(17p) or del(11q) (with indications for treatment initiation).

Workup

The workup for CLL/SLL is similar to the workup for other lymphoid neoplasms. Quantitative immunoglobulins may be informative in patients with recurrent infections. Measurement of beta-2 microglobulin may provide useful prognostic information.[32,34] Though classically, the pattern of bone marrow involvement (diffuse versus nodular) had prognostic significance, this is no longer a factor when one uses more reliable prognostic markers such as *IGHV* mutational status and cytogenetic abnormalities determined by FISH, all of which can be obtained by analysis of circulating lymphocytes. Thus, bone marrow biopsy is no longer considered a required part of the evaluation of patients with CLL though it remains useful to evaluate the etiology of cytopenias.

Computed tomography (CT) scans may be useful to follow and monitor disease progression when peripheral adenopathy is present. For anemic patients, reticulocyte counts and a direct Coombs' test should be performed to evaluate for the possibility of hemolysis. PET scan is generally not useful in CLL but can assist in directing nodal biopsy if Richter's transformation is suspected.

Staging

The nearly universal involvement of the bone marrow and peripheral blood in CLL/SLL limits the utility of the Ann Arbor staging system. Two staging systems, the Rai and Binet systems, are currently used worldwide in the evaluation of patients with CLL both in the routine practice and clinical trial settings.[59,60] Both staging systems rely solely on physical examination (presence of lymph node involvement, enlarged spleen and/or liver) and blood parameters (presence of anemia or thrombocytopenia) to assess the degree of tumor burden. The modified Rai classification stratifies patients into 3 risk groups.

Survival of patients with low-risk disease (Rai stage 0; median survival 150 months) is essentially the same as the survival rate of age-matched controls. Patients with intermediate-risk disease (Rai stage I-II; median survival 71-101 months) have a shorter survival, particularly when other adverse factors coexist, such as a lymphocyte doubling time of less than one year. Patients with high-risk disease (Rai stage III-IV; median survival 19 months) have a poor prognosis.[59] The Binet staging system is based on the number of involved areas and the level of hemoglobin and platelets and similar to the Rai staging system, provides meaningful correlation with clinical outcome.[60]

Response Criteria

The National Cancer Institute-sponsored Working Group (NCI-WG) on CLL published guidelines for the diagnosis and management of CLL in 1988 and 1996, primarily to facilitate consistency in the design and conduct of clinical trials. Most clinical trials of CLL reporting response outcomes have, until very recently, utilized the response criteria set forth in the 1996 NCI-WG guidelines.[61] In 2008, the NCI-WG guidelines were revised to reflect recent advances in our understanding of newer prognostic markers, diagnostic parameters, and treatments.[3] In particular, the 2008 guidelines provide further recommendations on the evaluations and response assessments appropriate for the general clinical practice setting versus for clinical trials.[3]

In the clinical practice setting, response assessment involves both physical examination and evaluation of blood parameters. For a complete response (CR), all of the following criteria must be met (at least 2 months after treatment completion): peripheral blood lymphocyte counts <4 ×10^9/L; absence of lymphadenopathy (i.e.,

palpable nodes must be ≤1.5 cm in diameter); absence of splenomegaly or hepatomegaly; absence of constitutional symptoms (i.e., weight loss, significant fatigue, fevers, night sweats); and normalization of blood counts without growth factor support (i.e., neutrophils >1.5 ×10^9/L, platelets >100 ×10^9/L, hemoglobin >11 g/dL).[3] For a partial response (PR), at least 2 of the following criteria must be met for at least 2 months duration: at least 50% reductions from baseline in peripheral blood lymphocyte counts, lymphadenopathy (based on sum of the products of multiple affected nodes), hepatomegaly, and/or splenomegaly; in addition, at least 1 of the blood counts should be normalized or increase by ≥50% from baseline, for at least 2 months duration.

In the clinical trial setting, CT scans are desirable for evaluations of adenopathy and organ involvement. In addition, also in the clinical trial setting, a bone marrow evaluation should be conducted to confirm a CR (<30% lymphocytes, normocellular morphology, absence of lymphoid nodules) if all other criteria for clinical CR (see above) are met. For patients who fulfill the criteria for a CR (including evaluation of the bone marrow) but present with persistent cytopenias due to treatment-related toxicities, these patients should be considered as having achieved a CR with incomplete marrow recovery (CRi).[3]

Progressive disease comprises any of the following: at least 50% increase from baseline in lymphocyte counts, lymphadenopathy, hepatomegaly, or splenomegaly, appearance of any new lesions, or occurrence of cytopenias attributable to disease (i.e., ≥50% decrease from baseline in platelet count, >2 g/dL decrease from baseline in hemoglobin levels).[3] Patients who do not have progressive disease but do not meet the criteria for a CR or PR are considered to have stable disease. Relapse is defined as evidence of disease progression after a period of 6 months or more following an initial CR or PR.

Refractory disease is defined as failure to achieve a response or having disease progression within 6 months of the last treatment.[3]

Treatment Options

During the last several decades, therapeutic options for CLL have evolved from the use of single-agent alkylating agents to purine analog-containing regimens and chemoimmunotherapy combinations. The advent of immunotherapeutic agents such as monoclonal antibodies that target cell surface antigens (e.g., CD20, CD52) and immunomodulating agents (e.g., lenalidomide) have led to the development of new and effective combination regimens that incorporate drugs with different mechanisms of action. A large number of clinical trials are currently ongoing to evaluate novel drug combination regimens, as well as investigational agents that target specific pathways of B-cell malignancies.

First-line Therapy

In an early clinical trial, the efficacy of chlorambucil plus prednisone was found to be comparable to that of CVP (cyclophosphamide, vincristine and prednisone) and CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) regimens in previously untreated patients with advanced CLL.[62] The randomized CALGB 9011 study evaluated first-line treatment with fludarabine, chlorambucil or the combination (N=509).[63] The combination arm was stopped early due to excessive toxicity; response rates were similar to fludarabine alone. Fludarabine, compared with chlorambucil, resulted in significantly improved CR rate (20% vs. 4%), PR rate (43% vs. 33%), median response duration (25 months vs. 14 months) and median PFS (20 months vs. 14 months). The study found no significant difference in median OS between the 2 arms (66 months vs. 56 months for chlorambucil), although it should be noted that these results included data from patients who crossed over from one

treatment arm to the other.[63] An European randomized study compared fludarabine with two alkylating agent-based combination regimens, CAP (cyclophosphamide, doxorubicin and prednisone) and CHOP as first-line treatment in patients with advanced CLL (N=938).[64] Fludarabine and CHOP produced similar overall remission rates (ORR; 71%) compared to CAP (58%); CR rates were significantly different between fludarabine (40%), CHOP (30%), and CAP (15%), although median survival times were similar (69, 67, and 70 months, respectively). Fludarabine was found to have a more preferable tolerability profile than CHOP.

Given that the median age of CLL diagnosis is 72 years (with approximately 70% of patients diagnosed at age ≥65 years),[65] the tolerability of a treatment regimen relative to a patient's physical fitness becomes an important consideration in the management of CLL. Older patients with CLL often present with comorbid conditions, which may decrease the patient's ability to tolerate certain regimens.[66] In a phase III randomized trial (CLL5 study) conducted by the German CLL Study Group, elderly patients (age >65 years; median age 70 years) were randomized to first-line treatment with fludarabine or chlorambucil (N=193).[67] Fludarabine, compared with chlorambucil, resulted in significantly improved ORR (72% vs. 51%), CR rates (7% vs. 0%), and median time to treatment failure (18 months vs. 11 months). However, no advantage with fludarabine was observed for PFS (median 19 months vs. 18 months) or OS (median 46 months vs. 64 months) outcomes.[67] Thus, in older patients (or in patients with comorbidities) with CLL for whom more intensive regimens are not appropriate, chlorambucil remains a valid treatment option.

The introduction of the anti-CD20 monoclonal antibody rituximab has led to important advances in the treatment of CLL, particularly in the context of combination regimens (see Discussion sections below). In the first-line treatment setting, rituximab as monotherapy resulted in modest activity with 51% ORR and 4% CR (based on the standard 4 weekly infusions; N=44); the median PFS was approximately 19 months.[68] Given the favorable tolerability profile, rituximab as single agent may be an appropriate treatment option for elderly patients with CLL who present with substantial comorbidities or decreased performance status. Rituximab has also been evaluated in combination with high-dose methylprednisolone (HDMP) in a small number of patients with previously untreated CLL (N=28).[69] The median age of the patients was 65 years, and a large proportion of patients had poor-risk factors at baseline (e.g., high-risk Rai stage in 48%; unmutated *IGHV* in 57%; cytogenetic abnormalities in 39%). Treatment with rituximab combined with HDMP resulted in 96% ORR with CR in 32% of patients. At a median follow up of 36 months, the median PFS was 30.5 months and OS rate was 96%.[69] In the small subgroup of patients aged >70 years (n=8), all patients responded and 3 patients achieved a CR (38%).

Two recent phase II studies reported outcomes with the combination of rituximab and chlorambucil as first-line treatment in patients with CLL, including in elderly patients.[70,71] In the multicenter Italian study (N=85 evaluable), elderly patients (age >60 years; median age 70 years) received induction therapy with chlorambucil combined with rituximab (up to 8 cycles); responders were subsequently randomized to receive rituximab maintenance (every 2 months for 2 years) or observation only.[70] Following induction therapy, the ORR was 81% with CR (confirmed by CT scan) in 16.5% of patients. The regimen was well tolerated, and treatment-related serious adverse events were reported in 7 patients (8%). The multicenter study from the UK (N=100) reported similar response outcomes and a favorable safety profile with chlorambucil combined with rituximab in previously

untreated patients (median age 70 years; range, 43-86 years); the ORR and CR rate was 80% and 12%, respectively.[71] Median PFS in this study was approximately 24 months. An ongoing randomized phase III study is evaluating first-line therapy with chlorambucil combined with rituximab versus chlorambucil alone (CLL11 study).

Obinutuzumab (formerly, GA101) is a type II humanized CD20 IgG1 monoclonal antibody with glycoengineering of the Fc region, and alterations to the elbow-hinge sequences of the antibody variable regions.[72] The engineered Fc region was shown to result in increased affinity to an activating Fc receptor (e.g., FcγRIII) expressed by immune effector cells such as NK cells.[72] In studies with normal and malignant B-cells, *in vitro,* obinutuzumab mediated superior induction of direct cell death as well as antibody-dependent cellular cytotoxicity (ADCC) compared with type I CD20 monoclonal antibodies (i.e., rituximab, ofatumumab).[72,73] Obinutuzumab was also more potent than the type I antibodies in whole blood B-cell depletion assays and more effective in terms of anti-tumor activity, *in vivo*, in lymphoma xenograft models.[72,73] However, consistent with the characteristics of a type II antibody, obinutuzumab showed reduced complement-dependent cytotoxicity (CDC), *in vitro*, in B-cell lymphoma cell lines compared with type I CD20 monoclonal antibodies.[72,73] In whole blood assays with CLL cells, induction of direct cell death, enhancement of NK cell activation and ADCC were reported as potential effector mechanisms of obinutuzumab.[74,75] This agent is currently under clinical evaluation for the treatment of B-cell malignancies including CLL.[76-79] In a small phase II study in patients with previously treated CLL (N=20; median 3 prior therapies, range 1–7), the ORR with single-agent obinutuzumab was 25%.[76] Half of the patients had received prior rituximab-containing therapies, and 25% had *TP53* mutations (among 14 patients evaluated for this genetic lesion). The most common grade 3 or 4 toxicities

included infusion-related reaction and neutropenia.[76] Several randomized phase III trials are underway to investigate the role of obinutuzumab in patients with CLL and B-cell lymphomas. A phase III trial of the GCLLSG (CLL11 trial) is comparing the efficacy and safety of obinutuzumab combined with chlorambucil (G+Clb) versus chlorambucil (Clb) alone (stage 1 of the trial) and versus rituximab combined with chlorambucil (R+Clb; stage 2) in previously untreated patients with CLL who have comorbidities (defined as CIRS score >6 and/or CrCl <70 mL/min).[77] The median CIRS score of patients in this study was 8, with approximately 75% of patients having scores greater than 6. In the first report from this study, G+Clb (n=238) showed an ORR of 75.5% (CR in 22%) compared with 30% (no CRs) in the Clb arm (n=118). The median PFS (primary endpoint) was significantly increased with G+Clb compared with Clb alone (23 mo vs. 10.9 mo; HR=0.14, 95% CI 0.09–0.21; *P*<0.0001), although the data are still immature with a limited observation time.[77] The 1-year PFS rate was 84% and 27%, respectively. The most frequent grade 3 or higher toxicities with G+Clb included neutropenia (34%), infusion-related reactions (21%), thrombocytopenia (11%) and infections (6%). In the rituximab arm of the trial, R+Clb (n=233) resulted in an ORR of 66% (CR in 8%) compared with 30% (no CR) in the Clb arm (n=118). The median PFS was also significantly increased with R+Clb compared with Clb alone (15.7 mo vs. 10.8 mo; HR=0.32, 95% CI 0.24–0.44; *P*<0.0001). The 1-year PFS rate was 63% and 27%, respectively. The most frequent grade 3 or higher toxicities with R+Clb included neutropenia (25%) and infections (8%).[77] Both combination regimens were more effective than Clb monotherapy. Obinutuzumab was recently approved (November 2013) by the FDA for the treatment of patients with previously untreated CLL in combination with chlorambucil. Further follow-up data from stage 2 analysis of the trial are awaited to determine the efficacy of the

combination regimen with obinutuzumab compared with rituximab in this CLL population.

For patients who are physically fit and do not present with substantial comorbidities, fludarabine constitutes the backbone for treatment regimens. In several large randomized phase III trials, the combination of fludarabine and cyclophosphamide (FC) was compared with fludarabine alone in relatively young patients (median age 58 to 64 years) with previously untreated CLL.[41,80,81] Combination chemotherapy with FC was associated with significantly improved ORR (74-94%), CR rates (23-38%) and PFS (median 32-48 months) compared with fludarabine alone.[41,80,81] No significant differences in OS outcomes were observed between treatment arms in these studies.

As previously mentioned, the advent of the anti-CD20 monoclonal antibody rituximab has led to the development of effective chemoimmunotherapy regimens in the treatment of CLL. The CALGB 9712 study evaluated the efficacy of fludarabine with concurrent or sequential administration of rituximab in untreated patients with CLL.[49,82] The concurrent regimen was associated with a higher ORR (90% vs. 77% for the sequential regimen) and CR rate (47% vs. 28%) at the expense of higher incidence of grade 3 or 4 toxicity (primarily comprising neutropenia and infusion-related events). Comparison of the outcomes of patients treated with fludarabine alone in the CALGB 9011 trial with the pooled results from the CALGB 9712 study suggested that the addition of rituximab to fludarabine prolongs PFS and OS.[83] The long-term follow up from the CALGB 9712 study (median follow-up time 117 months) reported a median PFS of 42 months (5-year PFS rate 27%) and median OS of 85 months.[49]

The combination of fludarabine, cyclophosphamide and rituximab (FCR) evaluated at M.D. Anderson Cancer Center as initial therapy (N=300) produced high ORR and CR rate.[31,84,85] At a median follow up of 6 years, the ORR was 95% (72% CR); the median time to progression was 80 months and the 6-year OS rate was 77%.[31] Recently, a large international randomized Phase III clinical trial (CLL8 study) showed that the addition of rituximab to fludarabine-based chemotherapy improved the outcome of patients with CLL with regard to response rates, PFS and OS compared to those receiving fludarabine-based chemotherapy alone.[40] In this trial, physically fit patients with previously untreated CLL (median age 61 years; N=817) were randomized to receive up to 6 courses of either FCR or FC regimen. The FCR regimen resulted in higher ORR (95% vs. 88%) and CR rate (44% vs. 22%) compared with FC. The median PFS was 52 months with FCR and 33 months with FC ($P<0.001$). At 3 years after randomization, the FCR regimen significantly improved both PFS rate (65% vs. 45%; hazard ratio [HR]=0.56, 95% CI 0.46–0.69; $P<0.0001$) and OS rate (87% vs. 83%; HR=0.67, 95% CI 0.48–0.92; $P<0.0001$) compared with FC alone. The FCR regimen was associated with significantly higher incidence of grade 3 or 4 neutropenia compared with FC (34% vs. 21%; $P<0.0001$); the incidence of severe infections and treatment-related deaths were similar between treatment arms. Based on the results of this trial, the FDA approved rituximab in combination with fludarabine and cyclophosphamide for patients with previously untreated CD20-positive CLL.

Pentostatin is another purine analog that has been evaluated as part of chemoimmunotherapy regimens in the first-line treatment of CLL. In a phase II trial initiated by two member institutes of the CLL Research Consortium, pentostatin, cyclophosphamide and rituximab (PCR) demonstrated significant clinical activity despite the large proportion of

patients with poor-risk prognostic factors (e.g., high-risk Rai stage in 53%; unmutated *IGHV* in 71%; FISH abnormalities in 52%) in this trial (N=64).[86] Responses were observed in 91% of patients (41% CR); median response duration (among responders) was 34 months. The median PFS for all patients on the trial was approximately 33 months.[86]. The toxicities were manageable, and appeared less myelotoxic relative to FCR regimens. A community-based multicenter phase III randomized trial (N=184) was conducted by US Oncology Research to compare the safety of PCR with FCR regimens in previously untreated (80% of patients) or minimally pretreated patients.[87] The ORR with PCR and FCR were similar (45% vs. 57.5%), with a lower CR rate in the PCR group (7% vs. 17%; *P*=0.04). The incidence of grade 3 or 4 infectious events and neutropenia were similar between treatment arms, with increased incidence of leukopenia and thrombocytopenia in the FCR group. [87] Overall, the PCR regimen did not appear to provide an advantage over FCR in terms of toxicity profile or clinical activity. A subsequent study investigated the possibility of reducing the toxicity of the PCR regimen by omitting cyclophosphamide (and using a higher dose of pentostatin) in previously untreated patients (N=33). [88] The combination of higher dose pentostatin with rituximab (PR) resulted in 76% ORR, with CR in 27% of patients.[88] Relative to historical outcomes with the PCR regimen, however, the response rates with PR were lower and the median treatment-free survival was also decreased (16 months vs. 30 months for PCR), suggesting that cyclophosphamide is an important component in the activity of PCR regimens.

Bendamustine is an alkylating agent with a purine-like benzimidazole ring component, and was found to exhibit low or incomplete cross-resistance with other alkylating agents due to its unique cytotoxic

properties.[89,90] In a pivotal phase III randomized study (N=319), the activity and safety of bendamustine was compared to chlorambucil in patients with previously untreated CLL.[91,92] Treatment with bendamustine, compared with chlorambucil, resulted in significantly higher ORR (68% vs. 31%; *P*<0.0001) and CR rate (31% vs. 2%; *P*<0.0001). After a median observation time of 54 months, the median PFS was significantly longer with bendamustine (21 months vs. 9 months; *P*<0.0001).[92,93] The higher response rates and PFS benefit with bendamustine was retained in the subgroup of older patients (age >65 years) on this trial.[94] Bendamustine was associated with higher incidences of grade 3 or 4 hematologic toxicities, infections, and gastrointestinal events compared with chlorambucil.[91] No differences in OS outcomes were observed between the two groups and the efficacy of bendamustine compared to first-line therapies other than chlorambucil has not yet been established. Bendamustine is also being evaluated as part of a chemoimmunotherapy regimen in patients with CLL. In a multicenter phase II trial (CLL2M study) from the German CLL Study Group, bendamustine in combination with rituximab (BR) showed high response rates (ORR 88%; CR 23%) in previously untreated patients (N=117), with similar response and survival outcomes among the subgroup of elderly patients (age >70 years).[95] The median duration of response was 31 months. After a median observation time of 27 months, the median PFS for all patients was 34 months, and OS rate was 90.5%. However, the BR regimen appeared to have limited activity in patients with del(17p). In the small subgroup of patients with del(17p) (n=8), the ORR (all partial remissions) was 37.5% and median PFS was only 8 months.[95] [96]The most common grade 3 or 4 toxicities included thrombocytopenia (22%), neutropenia (20%), anemia (20%), allergic/infusion reactions (9%), and infections (8%).[95] A phase III randomized trial is currently ongoing to compare outcomes between FCR and BR (CLL10 study). A phase III randomized trial is also ongoing

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to evaluate BR compared with rituximab combined with chlorambucil (R-chlorambucil) as first-line or second-line therapy in patients with CLL who are not suitable for fludarabine-based chemoimmunotherapy (due to older age or comorbid conditions). In an interim analysis of this trial, data from 126 patients (median age 74 years, range 44–91) were available for evaluation (BR, n=58; R-chlorambucil, n=68).[97] A higher proportion of patients in the BR group had poor-risk features including del(17p) / del (11q) (12% vs. 4%) and unmutated *IGHV* (53% vs. 38%) compared with the R-chlorambucil group. Among the patients who received first-line therapy (n=85), the ORR was 88% in the BR group (CR in 30%) and 80% (CR in 13%) in the R-chlorambucil group; these response rates were similar to data from the phase II studies with BR[95] and R-chlorambucil[70,71] in previously untreated patients with CLL. The toxicity profile was similar between treatment groups, with the most common grade 3 or 4 toxicity being neutropenia (BR, 32%; R-chlorambucil, 34%).[97]

Alemtuzumab, a humanized monoclonal antibody targeting CD52, was initially approved in the setting of fludarabine-refractory CLL (see Discussion section for "Relapsed/Refractory Disease" below), and has since shown clinical activity as a first-line treatment for patients with CLL (and is approved for this indication).[98,99 100-103] In an international, multicenter randomized phase III study (CAM307), previously untreated patients with CLL (N=297) were randomized to receive alemtuzumab or chlorambucil.[99] Alemtuzumab showed significantly higher ORR (83% vs. 55%; *P*<0.0001) and CR rate (24% vs. 2%; *P*<0.0001) compared with chlorambucil; in addition, a modest but statistically significant benefit in PFS was observed with alemtuzumab compared with chlorambucil (median 15 months vs. 12 months; HR=0.58, 95% CI 0.43-0.77; *P*=0.0001). In the small subgroup of patients (n=21) with del(17p), alemtuzumab showed numerically

higher ORR (64% vs. 20%) and longer median PFS (11 months vs. 2 months). Treatment with alemtuzumab was associated with higher incidence of infusion-related events, cytomegalovirus (CMV) infections and grade 3 or 4 neutropenia (41% vs. 25%) compared with chlorambucil; symptomatic CMV infection was reported in 16% of patients in the alemtuzumab arm. After a median follow up of 25 months, median OS has not been reached for either treatment arm; no significant difference in survival was reported between treatment arms.[99] Alemtuzumab is no longer commercially available for the treatment of CLL (although clinically available), and is not recommended as a first-line treatment option except in the setting of del(17p).

Lenalidomide, a thalidomide analog, is an immunomodulating agent indicated for the treatment of multiple myeloma and myelodysplastic syndromes. Lenalidomide has shown anti-tumor activity via its effects on the tumor microenvironment, including inhibition of angiogenesis, modulation of cytokine production, and activation of immune cells.[104-109] Several studies have evaluated first-line lenalidomide monotherapy. In a phase II study in patients with previously untreated CLL (N=25), lenalidomide (initial dose 2.5 mg daily, with dose escalation up to 10 mg daily; given 21 days of 28-day cycle) resulted in an ORR of 56% (all partial responses, no CRs) with a median duration of response of approximately 17 months at a median follow up of 21 months.[110] Tumor flare reactions occurred in 88% of patients but were all grade 1 or 2 events. The most common grade 3 or 4 toxicities included neutropenia (72%; grade 4 in 32%), thrombocytopenia (28%; grade 4 in 16%) and anemia (20%; grade 4 in 4%). Grade 3 or 4 infections or febrile events were reported in 36% (grade 4 febrile neutropenia in 8%). After an extended median follow up of 47 months, 52% of patients remain on therapy.[111] The 3-year

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PFS and OS rates were 69% and 85%, respectively. Recurrent myelosuppression was common during long-term treatment.[111] In another phase II study, lenalidomide (initial dose of 5 mg daily, with dose escalation up to 25 mg; given daily for 28 days of 28-day cycle) was evaluated in previously untreated patients 65 years or older (N=60).[112] In this study, the ORR was 65% with CR in 10% and incomplete CR (CRi; CR with residual cytopenias) in an additional 5% of patients. The median time to achieving a CR/CRi was 18 months (range, 9–27 months). After a median follow up of 31 months, the PFS and OS rates were 60% and 88%, respectively.[112] Interestingly, the subgroup of patients with unmutated *IGHV* (n=33) showed an ORR of 76% with a CR/CRi rate of 24%. Among the subgroup of patients with del(11q), the ORR was 64% with a CR/CRi rate of 21%. None of the patients with del(17p) had a response, and the median PFS in this poor-risk subgroup was only 6 months. The most common grade 3 or 4 toxicities included neutropenia (83%; grade 4 in 67%) and thrombocytopenia (47%; grade 4 in 8%). Grade 3 or 4 infections or febrile events were reported in 13% of patients. Tumor flare reactions (all grade 1 or 2 events) occurred in 52% of patients.[112] In an updated analysis from this study with a median follow up of 48 months, the median time to treatment failure had not been reached and the OS rate was 82%.[113] The updated analysis reported that 35 patients (58%) had achieved responses lasting 36 months or longer, and 25 of these patients were still on therapy; no deaths have occurred among the long-term responders.[113] Lenalidomide appeared to show promising activity in the front-line setting in CLL, particularly for older patients and for those with del(11q). Lenalidomide is also being evaluated in combination with other agents such as rituximab. In preclinical studies, lenalidomide was shown to increase the activity of NK cells, which in turn potentially augmented the antibody-dependent cellular cytotoxicity mediated by rituximab.[108,109] In a multicenter phase II study of the CLL

Research Consortium, previously untreated patients with CLL (N=69) were treated with lenalidomide (initial dose 2.5 mg daily, with dose escalation up to 10 mg daily; given 21 days of a 28-day cycle) combined with rituximab (dose escalated to 375 mg/m2 cycle 1; 375 mg/m2 weekly for 4 weeks in cycle 2, then on day 1 for cycles 3–7).[114] Patients in this trial were stratified by age group (age <65 years, n=40; age ≥65 years, n=29). Only 59% of the older patient group completed the planned 7 cycles of therapy compared with 90% of patients younger than 65 years. Tumor flare reaction occurred in 74% of patients, but was grade 1–2 in nearly all cases. The most common grade 3 or 4 toxicity was neutropenia, which was reported in 51% of patients. Neutropenic fever occurred in 4 patients (6%).[114] Among evaluable patients (n=57), the ORR in patients younger than 65 years (n=35) was 94% (CR in 20%) and the ORR in older patients (n=22) was 77% (CR in 9%). The median PFS in the younger patient group was 19 months after a median follow up of 17 months. The median PFS in the older patient group has not yet been reached given the short follow-up time; estimated PFS was 85% at a median follow up of 7 months.[114]

The phase III clinical evaluation of lenalidomide as first-line therapy in elderly patients (age >65 years) with CLL (ORIGIN trial) was recently halted by the FDA (in July 2013) due to concerns for increased risk of death in the lenalidomide arm versus the chlorambucil (comparator) arm.[115] At this time, lenalidomide cannot be recommended as a first-line treatment option (either as monotherapy or in combination regimens) in patients with CLL.

Relapsed or Refractory Disease
The FCR regimen has also been shown to induce high response rates in the relapsed/refractory disease setting.[116,117] In a phase II study evaluating FCR in patients with relapsed/refractory CLL (N=284;

median 2 prior therapies, range 1–10), the ORR was 74% with a CR rate of 30%.[117] The median PFS was 21 months and the estimated median survival was 47 months. The subgroup of patients with fludarabine-refractory disease (n=54) had significantly lower ORR (56% vs. 79%; *P*<0.001) and CR rate (7% vs. 39%; *P*<0.001) compared with fludarabine-sensitive patients; the median PFS (8 months vs. 28 months; *P*<0.001) and OS (38 months vs. 52 months; *P*<0.05) was also significantly decreased among patients with fludarabine-refractory CLL.[117] In addition, the subgroup of patients (n=20) with chromosome 17 abnormalities (based on standard karyotyping) had the worse outcomes with an ORR of 35% (no CR), median PFS of 5 months, and median survival of only 10.5 months. The investigators concluded that the patients most appropriate for therapy with FCR were those who were fludarabine sensitive, with no chromosome 17 abnormalities, and with fewer prior therapies (<4 prior regimens).[117] The most common adverse events with FCR were hematologic toxicities, including grade 3 or 4 neutropenia associated with 56% of treatment cycles and grade 3 or 4 thrombocytopenia in 19.5% of cycles. Pneumonia or sepsis was reported in 16% of patients.[117]. Recently, the phase III randomized REACH trial compared six cycles of FCR with six cycles of FC in patients with CLL at first relapse (N=552).[118] In this study, patients were excluded if they received prior FC (as a combination) or prior rituximab; moreover, patients were required to be fludarabine sensitive. After a median follow-up time of 25 months, patients in the FCR arm had significantly improved median PFS (based upon investigator assessment) compared with the FC arm (31 months vs. 21 months; *P*<0.001). The median PFS as assessed by an independent review committee also showed a significant benefit with FCR compared with FC (27 months vs. 22 months; *P*=0.022). Based on independent review committee evaluation, both the ORR (61% vs. 49%; *P*<0.005) and CR rate (9% vs. 3%; *P*<0.005) were significantly higher with the FCR

regimen. [118] At the time of follow up, OS was not significantly different between treatment regimens. Based on the results of this trial, the FDA approved rituximab in combination with fludarabine and cyclophosphamide for patients with previously treated CD20-positive CLL.

The combination of pentostatin and cyclophosphamide (PC) with or without rituximab (R) has shown significant activity in previously treated patients with relapsed or refractory CLL, including in patients with fludarabine-refractory disease.[119,120] In a small study in patients with relapsed/refractory CLL (N=23; median 3 prior therapies, range 1–5), the PC combination resulted in an ORR of 74% and CR rate of 17%; the ORR among patients with fludarabine-refractory disease was 77%.[120] In a study that evaluated the PCR regimen, the ORR and CR rate in the subgroup of patients with previously treated CLL (n=32) was 75% and 25%, respectively; the ORR among patients with fludarabine-refractory disease was 75%.[119] Thus, the response rates with the PC and PCR regimens appeared similar. However, based on a historical retrospective comparison, the median duration of response (25 months vs. 7 months) and median survival (44 months vs. 16 months) were longer with the PCR regimen compared with the PC regimen.[119]

In a phase I-II trial, the combination of oxaliplatin, fludarabine, cytarabine and rituximab (OFAR) was shown to be highly active in fludarabine-refractory patients with CLL (n=30) and those with Richter's syndrome (n=20).[121,122] The ORR was 50% in patients with Richter's syndrome and 33% in those with fludarabine-refractory CLL.[121] In addition, responses were achieved in seven (35%) of 20 patients with del(17p) and two (29%) of seven patients with del(11q). The median response duration was 10 months. The ORR in the subgroup of patients aged 70 years or older (n=14) was 50%.[121,122]

The German CLL Study Group recently conducted a phase II trial combining bendamustine and rituximab for patients with relapsed CLL (N=78; median 2 prior therapies, range 1–5) which resulted in an ORR of 59% and CR rate of 9%.[123,124] The ORR among the subgroup (n=22) with fludarabine-refractory disease was 45.5%. Among the patients with del(17p) (n=14), only 1 patient (7%) responded (with a CR). After a median follow up of 24 months, the median PFS and OS for all patients was 15 months and 34 months, respectively. Patients with del(17p) had the worse outcomes with a median PFS of 7 months and median survival of 16 months.[124] The most common grade 3 or 4 adverse events included hematologic toxicities (50% of patients) and infections (13%; all grade 3 events).[124] An ongoing phase III randomized trial is evaluating outcomes with BR compared with R-chlorambucil as first-line or second-line therapy in patients with CLL who are not suitable for fludarabine-based chemoimmunotherapy (due to older age or comorbid conditions). In an interim analysis of this trial, data from 126 patients (median age 74 years, range 44–91) were available for evaluation (BR, n=58; R-chlorambucil, n=68).[97] Among the patients who received second-line therapy (n=51; relapse occurred >12 months since last dose of first-line treatment), the ORR was 89% in the BR group (CR in 11%) and 83% (CR in 4%) in the R-chlorambucil group.[97]

High-dose methylprednisolone (HDMP) combined with rituximab has been shown to be well tolerated and an active therapy for patients with refractory CLL, including in those with unfavorable prognostic features. In several small studies, treatment with HDMP combined with rituximab resulted in ORR of 78-93% with CR in 14% to 36% of patients; median PFS (or time to progression) was 7-15 months, and one study reported a median survival of 20 months.[125-127] In addition, this regimen was shown to be active in patients with fludarabine-

refractory disease and/or del(17p).[125,126] The regimen was associated with infectious complications (including opportunistic fungal infections) in about 30% of patients,[125,127] which may necessitate adequate antiinfective prophylaxis and close monitoring for early signs of infections.

In an early phase II study, alemtuzumab was shown to induce significant responses in patients who were refractory to fludarabine based therapy (N=93).[128] The ORR with single agent alemtuzumab was 33% (CR 2%); median time to progression was 4.7 months for all patients (9.5 months for responders) and the median OS was 16 months (32 months for responders).[128] Several studies have also shown that alemtuzumab was effective in patients with fludarabine-refractory CLL with del(17p) or *TP53* abnormalities.[100-102,129] In a retrospective analysis, favorable ORR (49%), median PFS and survival outcomes (7 months and 19 months, respectively) were observed with alemtuzumab in pretreated patients with del(17p).[130] It should be noted that bulky lymphadenopathy does not typically respond well to alemtuzumab monotherapy in patients with refractory CLL.[128,131] Subcutaneous administration of alemtuzumab appeared as effective and safe as intravenous alemtuzumab in patients with advanced-stage relapsed or refractory CLL.[129,132-134] The most common grade 3-4 toxicities with alemtuzumab in the setting of heavily pretreated, relapsed/refractory disease included myelosuppression and infections.[128,131,134] Appropriate antiinfective prophylaxis and routine monitoring for early signs of infectious events are warranted when administering alemtuzumab-containing regimens. CMV reactivation can occur in about 10%-25% of patients with relapsed/refractory CLL treated with alemtuzumab.[128,131,134-136] It is therefore important to monitor for CMV antigenemia during alemtuzumab therapy. Combination regimens with alemtuzumab and

chemotherapy have been investigated with promising results in patients with relapsed/refractory CLL. In phase II and III studies, alemtuzumab combined with fludarabine (FluCam regimen) in relapsed CLL (primarily as second-line therapy) resulted in ORR of 82% to 85% and CR rates of 13% to 30%.[137,138] In the phase III randomized trial (N=335), the median PFS was significantly longer with FluCam compared with fludarabine alone (24 months vs. 16.5 months; P=0.003); infection rates were high, with 41% of patients in the FluCam arm experiencing infections (any grade, and including CMV reactivation) compared with 35% in the fludarabine arm.[138] Alemtuzumab has also been evaluated in combination with FC (FCCam regimen) in patients with previously treated CLL (N=56), which yielded an ORR of 68% (CR 22%); with this regimen, infections considered serious adverse events were reported in about 20% of patients.[139] Immunotherapy combination with alemtuzumab and rituximab has also shown promising results. In a phase II study in patients with relapsed/refractory CLL (N=40), alemtuzumab (using continuous infusion followed by subcutaneous administration) combined with rituximab resulted in ORR of 53% (CR 18%); infections (any grade, and including CMV reactivation) were reported in 28% of patients.[140] A more intensive chemoimmunotherapy regimen that combines cyclophosphamide, fludarabine, alemtuzumab and rituximab (CFAR) has been evaluated in a phase II study in patients with heavily pretreated relapsed/refractory CLL with high-risk features (N=80; median 3 prior therapies, range 1-14; 39% fludarabine-refractory).[141] The ORR with the CFAR regimen was 65% (CR 29%); median PFS and OS was 11 months and 17 months, respectively.[141] Although this regimen may be an option for some patients with high-risk disease, it was associated with a high rate of grade 3-4 infections (46%) and was not as active in the subgroup of patients with del(17p) (CR 14%;

median PFS 3 months) or fludarabine-refractory disease (CR 10%; median PFS 7 months).

Initial phase II studies of single-agent lenalidomide in patients with relapsed/refractory CLL showed ORRs of 32% to 47% and CR rates of 7% to 9%.[106,142] Among the subgroup of patients with del(11q), the ORR was 39% to 47%; the ORR in the small subgroup of patients with del(17p) was only 13%.[106,142] Tumor flare reactions occurred in 58% of patients (grade 3 or 4 in 8%).[142] The most common grade 3 or 4 toxicities included neutropenia (70%), thrombocytopenia (45%), anemia (18%) and febrile neutropenia (15%).[142] Lenalidomide was administered using different dosing schedules in these earlier studies. In one study, patients initially received lenalidomide at the 25 mg daily dose given intermittently (21 days of a 28-day cycle), which is the dosing schedule used for multiple myeloma; due to tumor lysis syndrome observed in the first patients on the study, the starting dose was reduced to 5 mg daily with subsequent dose escalation up to 25 mg daily.[142] In the other study, patients initially received lenalidomide at a dose of 10 mg daily given continuously for 28 days of a 28-day cycle; the dose was escalated up to a maximum of 25 mg daily.[106] No tumor lysis was reported in this latter study. Studies showed that in patients with CLL, the "standard" 25 mg dose of lenalidomide used in patients with multiple myeloma resulted in excessive toxicity (tumor flare, tumor lysis and myelosuppression) when given as the initial dose.[104,110,142] More recently, lenalidomide was investigated in combination with rituximab in patients with relapsed/refractory disease. A phase II study evaluated lenalidomide (initial dose 10 mg daily started on day 9 of cycle 1; given 28 days of a 28-day cycle) combined with rituximab (375 mg/m^2 weekly for 4 weeks in cycle 1, then on day 1 of cycles 3–12) in patients with relapsed/refractory CLL (N = 59; median 2 prior regimens).[143,144] The ORR was 66% with CR in 12%; all CRs were observed after 12 or more

cycles of therapy. The median time to treatment failure was 17 months for all patients. The median OS has not been reached, with an estimated 3-year OS rate of 71%. Among the subgroup of patients with del(17p) (n = 15), the ORR was 53%, which was not significantly different from the 70% ORR among patients without del(17p). However, the subgroup of patients considered fludarabine refractory (n = 12) had decreased ORR compared with those who were sensitive (33% vs. 70%; *P*=0.04). In addition, patients with del(17p) who were also fludarabine refractory had the worse survival outcomes, with a median OS less than 10 months. The most common grade 3 or 4 toxicity included neutropenia (74%), thrombocytopenia (34%), and infections or febrile episodes (24%). Tumor flare reactions occurred in 27% of patients, but were all grade 1 or 2 events.[144]

The treatment of patients with fludarabine-refractory CLL remains a challenge, particularly for patients who do not respond with alemtuzumab therapy. Ofatumumab is a human CD20 monoclonal antibody with activity in patients with fludarabine-refractory CLL also refractory to alemtuzumab or considered unsuitable for alemtuzumab therapy due to bulky lymphadenopathy.[145] In the final analysis from the pivotal international clinical trial, which included data from 206 patients with fludarabine- and alemtuzumab-refractory (FA-ref; n=95) CLL or patients with fludarabine-refractory CLL with bulky lymphadenopathy (BF-ref; n=111), ofatumumab therapy resulted in an ORR of 51% in the FA-ref and 44% in the BF-ref patients.[145] The median PFS was 5.5 months for both groups, and the median OS was 14 months and 17 months for the FA-ref and the BF-ref groups, respectively. The most common ≥grade 3 adverse events were infections (24%) and neutropenia (12%).[146] Ofatumumab is currently approved in the US and EU for the treatment of CLL refractory to fludarabine and alemtuzumab.

Allogeneic hematopoietic stem cell transplant (HSCT) has been evaluated to improve the prognosis in patients with advanced disease and those with poor-risk features.[147-153] In a retrospective analysis of the European Group for Blood and Marrow Transplantation (EBMT), allogeneic HSCT induced long-term remission in patients with del(17p).[152] At a median follow-up period of 39 months, 3-year PFS and OS rates were 37% and 44%, respectively. The final results of the prospective multicenter trial (GCLLSG CLL3X study) also showed that nonmyeloablative allogeneic HSCT can induce sustained MRD-negative event-free survival (EFS) in a significant proportion of patients with poor-risk CLL (defined as refractoriness or early relapse to purine analog-containing therapy, relapse after autologous SCT, disease progression with presence of unfavorable genomic abnormalities).[153,154] The 4-year EFS and OS rates for patients who underwent HSCT in this study (N=90) was 42% and 65%, respectively; 52% of patients had MRD negativity at 12 months post-HSCT.[154] The 4-year non-relapse mortality rate was 23%. The 4-year EFS and OS rates for the subgroup of patients with del(17p) (n=13) was 45% and 59%, respectively, and was not significantly different from the survival rates of patients without del(17p). Moreover, 6 of 13 patients (46%) with del(17p) achieved durable MRD-negative remissions.[154] It is understood that studies involving allogeneic HSCT are subject to strong selection biases. Nonetheless, available evidence from non-randomized clinical studies suggest that allogeneic HSCT may be an effective treatment option for patients refractory to chemoimmunotherapy or who develop recurrence within 12 months after purine analog treatment.[155]

Consideration of Functional Status and Comorbidity
CLL primarily affects the elderly, with a median age at diagnosis of 72 years; approximately 70% of patients are diagnosed at age ≥65 years (and 40% diagnosed at age ≥75 years).[65] Although

chemoimmunotherapy regimens such as FCR are now considered the standard of care for younger or physiologically fit patients (so called "go-go" patients) with CLL,[40] older patients who are not as fit (but may still benefit from active therapy) often cannot tolerate aggressive regimens due to decline in organ function and/or coexisting disease (so called "slow-go" patients).[66] In the only completed phase III randomized trial (CLL5 study) that specifically enrolled elderly patients with CLL (age ≥65 years; N=193) to evaluate treatment (first-line fludarabine vs. chlorambucil), 65% of patients presented with at least 1 coexisting condition, and about a third of patients had 2 or more comorbidities at the time of study enrollment.[67] As discussed earlier, treatment with fludarabine was not superior to chlorambucil in terms of PFS or OS outcomes. In this trial, elevated serum beta-2-microglobulin and presence of 2 or more comorbidities were significant independent factors for shorter PFS and OS based on multivariate analyses. The presence of multiple comorbidities was a negative prognostic factor independent of disease stage or age.[67] Several retrospective studies have also reported on the negative impact of comorbidities on patient outcomes in CLL.[156-158] The most common comorbidities reported include hypertension (19–53%), coronary artery disease (7–24%), hyperlipidemia or lipometabolic disease (16–38%), and diabetes mellitus (10–21%).[156-158]

These findings underscore the need to assess comorbidities, in addition to patient age and performance status, when evaluating the overall "fitness" of an individual patient. Comorbidities are frequently present in older patients, and organ function (e.g., kidney, liver) as well as bone marrow reserve decline with increasing age. These physiological factors must be considered when weighing therapeutic options for individual (especially older) patients, as the metabolic or elimination pathways of certain agents may influence their toxicity profile and tolerability.

Various tools and scoring systems are available to assess comorbidities in patients with CLL, including the Cumulative Illness Rating Scale (CIRS), Charlson Comorbidity Index, and the NCI Comorbidity Index.

NCCN Recommendations

Localized SLL (Ann Arbor stage I)
Locoregional radiation therapy (RT) is an appropriate induction therapy for this group of patients. In rare cases, RT may be contraindicated or may be a sub-optimal therapy due to the presence of comorbidities or the potential for long-term toxicity. Patients with localized SLL that has progressed after initial RT are treated as described below for patients with SLL (Ann Arbor stage II–IV).

SLL (Ann Arbor stage II-IV) or CLL (Rai stages 0-IV)
Early stage disease in some patients may have an indolent course and in others may progress rapidly to advanced disease requiring immediate treatment. A "watch and wait" approach is often appropriate for patients with early stage, low-risk disease (Rai stage 0; Binet A) in the absence of disease symptoms. Patients with Binet B or intermediate-risk disease (Rai stage I or II) may benefit from therapy if they show evidence of progressive disease or they become symptomatic.[3] Absolute lymphocyte count alone is not an indication for treatment unless it is above 200 to 300 × 10^9/L or symptoms related to leukostasis occur. Indications for initiating treatment include the following[3]: significant disease related constitutional symptoms including severe fatigue, weight loss, night sweats and fever without infection; threatened end-organ function; progressive bulky disease (enlarged spleen or lymph nodes); progressive bone marrow failure (with development or worsening of anemia or thrombocytopenia); or autoimmune anemia/thrombocytopenia unresponsive to corticosteroids. Asymptomatic patients should be observed until such indications (as mentioned above) become apparent, or be considered for clinical trials,

as appropriate. Patients with advanced stage or high-risk CLL (Binet C; Rai stage III-IV) will typically present with symptomatic disease and will require immediate treatment.

Given the incurability of the disease, the NCCN Guidelines recommend enrollment in clinical trials, when locally available, as the preferred therapy for all patients. In the absence of suitable clinical trials, the treatment recommendations included in the Guidelines are based on factors such as the overall fitness of a patient (comorbidity index/performance status), presence or absence of high-risk genomic abnormalities [del(17p) or del(11q)], and patient age.. For patients requiring treatment for symptomatic disease, the NCCN panel recommends that patients be stratified according to functional status and comorbid conditions. Comorbidities can be assessed using published tools such as the CIRS.[159] Patients who are frail or who present with significant comorbidity (the "no go" patients) that preclude treatment with purine analogs should be treated with palliative therapy (see below). Patients who have adequate functional status can be treated with more active or intensive therapies, and should be evaluated for cytogenetic abnormalities by FISH. The presence or absence of del(17p) and del(11q), as well as patient age, should then help to direct treatment options, as shown below.

Frail Patients with Significant Comorbidity

For frail patients with significant comorbidities and not able to tolerate purine analogs, the options include treatment with chlorambucil (with or without rituximab), rituximab monotherapy or pulse corticosteroids.

CLL without del(17p)or del(11q)

First-line Therapy

For patients 70 years or older or younger patients with significant comorbidities, the NCCN Guidelines have included alkylating agent-based chemoimmunotherapy (eg, chlorambucil with or without rituximab, bendamustine with or without rituximab), rituximab monotherapy, fludarabine with or without rituximab, or cladribine as options. For patients 70 years or younger, or for older patients without significant comorbidities, the NCCN Guidelines have included rituximab in combination with purine analog-based chemotherapy (FCR, FR, PCR) or bendamustine with or without rituximab as options (see Guidelines section under "Suggested Treatment Regimens: CLL without del(17p)or del(11q)" for a list of specific regimens).

In patients younger than 70 without significant comorbidities chemoimmunotherapy has emerged as the standard of care.[40,49] A randomized comparison of FCR versus PCR demonstrated a higher CR rate for FCR but the ORR and survival were no different between the regimens.[87] Both FCR and FR are highly active regimens, however, we do not have category 1 evidence to designate one as the preferred regimen over the other. In the absence of del(11q), it is uncertain whether there are differences in long-term outcomes between these regimens.

Although the oral formulation of fludarabine has been investigated[160-162] and is approved by the FDA for the treatment of CLL (in patients who have not responded to or have progressed after treatment with at least one alkylating agent), its use in combination regimens for CLL has not yet been established. Moreover, no prospective randomized trials have evaluated the activity and safety of the oral formulation

compared with IV fludarabine. Therefore, the NCCN Guidelines panel cannot recommend the appropriate use of oral fludarabine at this time.

Second-line Therapy

For patients relapsing after or refractory to first-line therapy, treatment options are dependent on the duration of response following the first-line treatment regimen. Among patients who failed FCR chemoimmunotherapy as initial therapy, those with a time to treatment failure of 3 years or more had better median survival (44 months) than those with a time to treatment failure of less than 3 years (12 months).[163] If the response to first-line treatment is of long duration, the NCCN Guidelines panel recommends retreatment with the same regimen that was used as first-line therapy for all patients.

If the response is of short duration, treatment options are dependent on the patient's age and presence of comorbid conditions. In the setting of a short response, regimens other than those administered as first-line therapy should be considered. For patients 70 years or older or for younger patients with comorbidities, options include reduced-dose FCR or PCR, bendamustine with or without rituximab, HDMP with rituximab, chlorambucil with or without rituximab, monotherapy with ofatumumab, lenalidomide with or without rituximab, alemtuzumab with or without rituximab, or dose-dense rituximab. For patients younger than 70 years or for older patients without significant comorbidities, the NCCN Guidelines have included chemoimmunotherapy (eg, FCR, PCR, bendamustine with or without rituximab, fludarabine with alemtuzumab, CHOP with rituximab, OFAR), monotherapy with ofatumumab, lenalidomide with or without rituximab, alemtuzumab with or without rituximab, or HDMP with rituximab as suggested options (see Guidelines section under "Suggested Treatment Regimens: CLL without del(17p)or del(11q)" in the for a list of specific regimens). It should be noted that long and short response durations cannot be rigorously

defined based on currently available data. A major factor in evaluating the durability of a response is that the definition would be influenced by the prior treatment regimen. Therefore, physicians will need to exercise clinical judgement for individual cases. For instance, after a regimen such as FCR, response duration of 3 years may be a reasonable cutoff based upon data from the MD Anderson Cancer Center. However, after treatment with a less intensive regimen such as single-agent chlorambucil, response duration of 18-24 months may be a more reasonable cutoff.

Allogeneic HSCT can be considered for a select population of patients (without significant comorbidities) with short responses to chemoimmunotherapy regimen, but would generally be considered after re-induction of remission.

CLL with del(17p)

No standard treatment exists for patients with del(17p), as outcomes remain poor with currently available treatment regimens. Therefore, enrollment in an appropriate clinical trial is particularly recommended for patients with del(17p). In the absence of appropriate clinical trials in the patient's local area, suggested first-line therapy options include FCR or FR, HDMP plus rituximab, or alemtuzumab with or without rituximab.

Patients who have achieved CR or PR to first-line therapy should be considered for allogeneic HSCT, if they are eligible. Patients with CR or PR following transplant can either be observed or enrolled in clinical trials. Alternatively, patients with PR could also be treated with chemoimmunotherapy.

Patients with no response to first-line therapy, patients who respond to first-line therapy but are not eligible for allogenic HSCT and for those

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with no response to transplant should be enrolled in clinical trials or be treated with second-line therapy for relapsed or refractory disease. The NCCN Guidelines have included chemoimmunotherapy regimens, monotherapy with ofatumumab, lenalidomide with or without rituximab, alemtuzumab with or without rituximab, or HDMP with rituximab as options (see Guidelines section "Suggested Treatment Regimens: CLL with del(17p)" for a list of specific regimens).

CLL with del(11q)

First-line therapy options are based on the patient's age and associated comorbid conditions. For patients with a del(11q) abnormality, an alkylating agent should be included in the treatment regimen. In patients older than 70 years of age or with significant co-morbidities, first-line treatment options include chlorambucil with or without rituximab, bendamustine with or without rituximab, cyclophosphamide and prednisone with or without rituximab,, reduced-dose FCR, or rituximab monotherapy; however, single agent rituximab should only be used if an alkylator is contraindicated or considered intolerable. For patients younger than 70 years of age or for older patients without significant comorbidities, first-line treatment options include FCR, bendamustine with or without rituximab or PCR.

Patients who have achieved CR to first-line therapy can either be observed until disease progression or enrolled in clinical trials. For those with disease progression following CR, treatment options are dependent on the duration of response to first-line therapy (similar to regimens discussed under "Second-line Therapy" above; also see Guidelines section "Suggested Treatment Regimens: CLL with del(11q)" for a list of specific regimens). Participation in a clinical trial is also a consideration in this setting. Patients with PR to first-line therapy should be considered for allogeneic HSCT, if they are eligible.

Following transplant, treatment options are similar to those described for patients with del(17p).

Patients with no response to first-line therapy, patients with PR to first-line therapy but are not eligible for allogenic HSCT should be enrolled in clinical trials or can be treated with second-line therapy for relapsed or refractory disease (see Guidelines section "Suggested Treatment Regimens: CLL with del(11q)" for a list of specific regimens).

Histological Transformation to DLBCL or Hodgkin lymphoma

About 2% to 5% of patients with CLL will develop Richter's syndrome (transformation into DLBCL or Hodgkin lymphoma) during the course of the disease and treatment.[164-166] The incidence of transformation increases with the number of prior regimens. Patients with Richter's syndrome should be treated with a combination of chemoimmunotherapy regimens initially developed for DLBCL.[167]

Allogeneic HSCT has also shown promising results in patients with Richter's syndrome. In a non-randomized comparative analysis, the estimated cumulative 3-year survival rate was significantly higher (75%) for patients who underwent allogeneic SCT after achieving CR or PR to initial therapy compared with those who responded to initial therapy but did not undergo allogeneic SCT, or who underwent allogeneic HSCT for relapsed or refractory Richter's syndrome (75% vs. 27% and 21%, respectively; P=0.019)).[167] Thus, allogenic HSCT can be a consideration following a response to initial therapy in patients with Richter's syndrome.

Investigational Agents in CLL

The treatment of hematologic malignancies is an evolving field, and the last few years have seen rapid advancements in the development of potential new agents that hold promise in the treatment of patients with

B-cell malignancies including CLL. These investigational agents include small molecule inhibitors of anti-apoptotic proteins and small molecule inhibitors of the B-cell receptor (BCR) signalling pathway. It should be noted that these agents are investigational, and not yet approved by the FDA for use in any indication.

Bcl-2 Inhibitors

The anti-apoptotic members of the Bcl-2 family of proteins (e.g., Bcl-2, Bcl-xL, Bcl-w, Mcl-1) inhibit the activation of proteins involved in the apoptotic pathway.[168] Bcl-2 is highly expressed in CLL cells, and thereby represents a potential therapeutic target.[169-171] Several small molecule inhibitors of Bcl-2 are under development. ABT-263 (navitoclax) is an orally administered inhibitor of Bcl-2 and related proteins, and demonstrated single-agent activity in patients with relapsed/refractory CLL.[170] This agent, however, was found to be associated with dose-limiting thrombocytopenia given its inhibition of Bcl-xL required for platelet activation.[170,172] ABT-199 is a structural analogue of navitoclax, and specifically inhibits Bcl-2 while sparing Bcl-xL activity.[173] This agent was shown to inhibit the growth of Bcl-2-expressing tumors *in vivo* without causing thrombocytopenia.[173,174] In whole blood assay from patients with CLL, ABT-199 was found to selectively and potently induce apoptosis in CLL cells without affecting platelets; this was in contrast to ABT-263, which resulted in substantial apoptosis of platelets.[171] In a phase I dose-escalation trial in patients with relapsed/refractory CLL (N=56; median 3.5 prior therapies, range 1–10), grade 3 or 4 thrombocytopenia was reported in 11% of patients.[175] Other grade 3 or 4 toxicities included neutropenia (38%) and tumor lysis syndrome (TLS; 9%); 1 fatal case of TLS was reported. Among evaluable patients (n=54), the ORR was 85% with a CR (or CRi) in 13% of patients. Response was observed in the subgroup of patients with high-risk features such as del(17p)(n=16; ORR 88%) and fludarabine-refractory disease (n=16; ORR 75%).[175]

Inhibitors of BCR Signaling Pathways

Several novel agents that target specific signaling pathways are under active investigation. B cells rely on signaling events mediated by BCR for their maturation, proliferation, survival and cell death.[176,177] Activation of the BCR triggers a cascade of signaling events, including activation of key tyrosine kinases that regulate B-cell development and function. The role of several such tyrosine kinases involved in BCR signaling has been investigated, including the spleen tyrosine kinase (SYK),[178-180] PI3 kinase (PI3K)[181-183] and Bruton tyrosine kinase (BTK).[182,184-187] These kinases represent potential novel targets for the treatment of B-cell malignancies.

Overexpression of SYK has been reported in CLL cells, and SYK activation has been shown to be involved in the migration and adhesion of CLL cells in tumor microenvironments that may promote their survival.[179,188] Inhibition of SYK has been reported to induce apoptosis in malignant B cells (including primary CLL cells) *in vitro*, inhibit migration and tissue homing pathways *in vitro*, as well as induce tumor regression in animal models of B-cell disease.[178-180,189-192] Small molecule inhibitors that target SYK, PI3K (the delta isoform, specifically), and BTK have been developed, and are currently under clinical evaluation. In early clinical studies, the SYK inhibitor fostamatinib showed clinical activity in patients with relapsed/recurrent B-cell malignancies, including those with CLL.[193] Other specific small molecule inhibitors of SYK are expected to enter clinical evaluations in the near future.

PI3K is involved in the regulation of cell functions such as cell development, proliferation, survival and migration.[181,183] Inhibition of PI3K-delta has been shown to induce apoptosis of CLL cells and other B-cell lines, as well as decrease CLL cell survival by reducing cellular interactions that promote survival of these malignant cells.[194-196]

The isoform-selective oral inhibitor of PI3K-delta, idelalisib (formerly, CAL-101/GS-1101), has demonstrated promising clinical activity in phase I-II studies in patients with CLL, both as monotherapy[197] and in combination with existing agents such as rituximab and bendamustine.[198,199] In a phase I study of idelalisib in patients with heavily pretreated relapsed/refractory CLL (N=54; median 5 prior therapies, range 2–14), cohorts received continuous oral dosing of idelalisib 50 to 350 mg BID (one of the cohorts was given 300 mg QD) for 48 weeks; treatment could be extended for patients deriving clinical benefit.[197] A large proportion of patients on this trial had high-risk prognostic features including unmutated *IGHV* (91%), del(17p) and/or *TP53* mutations (25%) and del(11q)(28%). The ORR with idelalisib as single agent was 39%. In addition, another 33% of patients achieved a PR with lymphocytosis based on updated response criteria.[200] Lymph node response was observed in 81% of patients. Notably, the rapid reduction in lymphadenopathy was observed with a concomitant increase in lymphocyte counts, which decreased with continued treatment. The median PFS for all patients was 17 months. Among the cohort of patients who received idelalisib using a dose schedule of 150 mg BID or greater, the median PFS was 29 months.[197] The most common grade 3 or greater adverse event was pneumonia (18.5%), neutropenic fever (11%) and diarrhea (6%).[197] In a phase I study of idelalisib (150 mg BID continuously) combined with rituximab (275 mg/m² weekly for 8 weeks) or bendamustine (70 or 90 mg/m²/day for 2 days, every 4 weeks for 6 cycles) or with BR, in patients with relapsed/refractory CLL (N=51; median 3 prior therapies, range 1–9), the combined regimen resulted in an ORR of 84% (CR in 1 patient).[201] Nearly all patients (98%) had received prior rituximab-containing therapies and 45% had received prior bendamustine. The median duration of idelalisib-containing treatment regimen was 18 months. The 2-year PFS and OS rates were 65% and 85%, respectively. The most

common grade 3 or greater adverse events included diarrhea (14%), pneumonia (12%) and laboratory-evaluated ALT/AST elevation (8%).[201]

A phase II study evaluated the combination of idelalisib with rituximab in elderly patients (age ≥ 65 years) with previously untreated CLL (N=64; median age 71 years, range 65–90).[199] Idelalisib was given at a dose of 150 mg BID continuously for 48 weeks (could be extended for patients deriving benefit) and rituximab was administered at a dose of 375 mg/m² weekly for 8 weeks. High-risk disease features included presence of *IGHV* mutation (58%), del(17p) and/or *TP53* mutations (14%) and del(11q)(20%). The median duration of idelalisib treatment was 14 months. The ORR was 97% with a CR in 19% of patients. Among the subgroup with del(17p) and/or *TP53* mutations (n=9), the ORR was 100% with a CR in 33%.[199] The median PFS has not been reached with current follow up; the estimated PFS at 24 month was 93%. In contrast to the pattern observed with single-agent idelalisib in CLL, a steady reduction in lymphocyte count was observed with no initial rise in lymphocytosis. The most common grade 3 or greater adverse event included diarrhea (23%; reported as grade 3 colitis in 10 cases) and pneumonia (17%). The most common grade 3 or greater laboratory-evaluated toxicity was elevated ALT/AST (28%) and neutropenia (23%).[199]

Several phase III clinical trials are currently underway to evaluate the role of idelalisib in combination regimens (rituximab, ofatumumab, BR) in patients with previously treated CLL.

BTK is activated by SYK, and plays a key role in B-cell development and proliferation, as well as in the migration and homing involved in the interaction of B-cells with the tissue microenvironment.[182,184,185,187] Inhibition of BTK has been shown to decrease the proliferation of malignant cells *in vitro* (including reduced survival of CLL cells), block

survival signals from the tumor microenvironment, prevent CLL cell migration in response to homing signals, and result in tumor regression in animal models of B-cell lymphomas and CLL.[186,202-204]

The selective and irreversible oral BTK inhibitor ibrutinib has shown remarkable single-agent activity with a favorable toxicity profile in phase I/II studies in patients with relapsed/refractory B-cell malignancies including CLL,[205-207] as well as in previously untreated, elderly patients with CLL.[205] A phase I study evaluated ibrutinib given as an intermittent dose (1.25–12.5 mg/kg daily for 28 days of a 35-day cycle) or continuous dose (8.3 mg/kg or 560 mg daily until disease progression) in previously treated patients with NHL or CLL (N=56; median 3 prior therapies, range 1–10).[206] The maximum tolerated dose of ibrutinib was not reached. The most common grade 3 or 4 adverse events included neutropenia (12.5%), thrombocytopenia (7%), anemia (7%) and respiratory (non-cough) toxicities (7%). The ORR was 54%. The median PFS was 13.6 months. In the subgroup of patients with CLL (n=16), the ORR was 69% with a CR in 12.5% of patients; transient increase in lymphocyte count was observed in patients with CLL. The fixed dose of 560 mg daily given continuously was well tolerated and resulted in full occupancy of the BTK target.[206] A phase Ib/II trial evaluated single-agent ibrutinib (420 mg or 840 mg daily until disease progression) in previously untreated patients (age ≥ 65 years; n=31) and those with relapsed/refractory (n=61) or high-risk CLL (defined as having del(17p) or relapse within 24 months of chemoimmunotherapy; n=24).[205] Grade 3 or greater toxicities were infrequent. The ORR was 71% in previously untreated elderly patients (CR in 10%), 67% in relapsed/refractory patients (CR in 3%) and 50% (all PRs) in high-risk patients. In addition, PR with lymphocytosis was observed in another 10%, 20%, and 29% of patients, respectively. The estimated PFS at 22 months was 96% for previously untreated elderly patients and 76% for the

relapsed/refractory or high-risk CLL cohorts. The estimated OS at 22 months was 96% and 85%, respectively.[205] In the full report of the relapse/refractory and high-risk cohorts from this study (N=85; median 4 prior therapies, range 1–12), a large proportion of patients had high-risk features including unmutated *IGHV* (81%), del(17p)(33%) and del(11q)(36%).[207] The ORR was 71% with a CR in 2% of patients. PR with lymphocytosis was observed in another 18% of patients. The ORR was the same (71%) in the two dose groups. Among the subgroup with del(17p)(n=28), the ORR was 68% (CR in 3.5%). The estimated PFS and OS at 26 months was 75% and 83%, respectively.[207] Reduction in lymphadenopathy was accompanied by initial increase in lymphocyte counts. The most common grade 3 or 4 adverse events included neutropenia (15%), pneumonia (12%), thrombocytopenia (6%), dehydration (6%), sinusitis (5%), fever (5%) and hypertension (5%).[207] This study showed durable remissions with single-agent ibrutinib in a high proportion of patients with relapsed/refractory CLL. Importantly, ibrutinib appears to maintain anti-tumor activity in patients with high-risk prognostic features. This agent has received 'breakthrough' designation by the FDA for the treatment of CLL with del(17p). Ongoing phase Ib/II trials with ibrutinib (420 mg daily) combined with BR[208] or ofatumumab[209] in patients with relapsed/refractory CLL has shown promising early results with high response rates (ORR 90–100%).

Several phase III clinical trials are currently underway to evaluate the role of idelalisib as single-agent therapy and as part of combination regimens in patients with CLL. Ibrutinib is under investigation as monotherapy in relapsed/refractory CLL (versus ofatumumab) or in previously untreated elderly patients with CLL (versus chlorambucil). Another ongoing phase III trial is evaluating ibrutinib alone compared with the BR regimen or ibrutinib combined with rituximab in previously untreated elderly patients with CLL. In addition, a phase III trial is

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investigating the combination of ibrutinib with the BR regimen (versus BR alone) in patients with relapsed/refractory CLL.

Interestingly, the use of these novel tyrosine kinase inhibitors (i.e., idelalisib or ibrutinib) as monotherapy is associated with an initial transient increase in lymphocytosis in the majority of patients with CLL treated with these agents. This phenomena is thought to result from the redistribution or release of leukemic cells from the lymph node compartment to the peripheral blood.[210] To account for these findings, recommendations for revised response assessment for treatment of CLL with immunomodulating agents or BCR inhibitors were recently published.[200] The proposed recommendations would allow for a new response category, "PR with lymphocytosis," to include patients with a clinical response (reduction in lymph nodes and splenomegaly) to BCR inhibitors but with persistent lymphocytosis (in the absence of other indicators of progressive disease).[200]

Supportive Care for Patients with CLL

Infections
Patients with CLL are susceptible to infectious events due to both the underlying disease and treatment with immunosuppressive agents. Infectious complications are influenced by the reduction in immunoglobulin levels and are more common in previously treated patients.[211] Hypoglobulinemia has been shown to be present in about 40% of patients up to 3 years prior to diagnosis of CLL.[212] Heavily pretreated patients who become refractory to fludarabine have high susceptibility to developing serious infections. In a retrospective analysis, 89% of patients with fludarabine-refractory CLL developed infectious complications requiring hospitalization.[213] Administration of IVIG (for recurrent infections and if IgG levels <500 mg/dL), antiinfective prophylaxis and vaccinations are the main options available to minimize the possibilities of developing infectious complications.

In randomized studies, IVIG has been associated with a significant decrease in the occurrence of infections but with no improvement in survival outcomes.[214-218] Antibacterial prophylaxis may be a useful alternative option. Protein and conjugate vaccines have been shown to induce better responses than plain polysaccharide vaccines.[219,220] Some studies have reported that histamine type-2 (H2) receptor blockers can enhance vaccine response.[221,222]

In selected patients (serum IVIG <500 mg/dL) with recurrent sinopulmonary infections requiring intravenous antibiotics or hospitalization, the Guidelines recommend monitoring IVIG levels and administering monthly IVIG (0.3-0.5 g/kg) to maintain nadir levels of approximately 500 mg/dL. The use of antiinfective prophylaxis is also appropriate for the management of patients who may be susceptible to certain infections due to a given treatment regimen. Antiviral and pneumocystis prophylaxis is recommended for patients receiving purine-analog and/or alemtuzumab during treatment and thereafter. Acyclovir or equivalent is recommended for herpes virus and sulfamethoxazole trimethoprim or equivalent is recommended for *Pneumocystis* pneumonia (PCP) prophylaxis. Annual influenza vaccine and pneumococcal vaccine (every 5 years) is recommended for all patients. All live vaccines should be avoided. Patients with CLL tend to have a poor response to influenza vaccine and should be counseled to exercise care during influenza season even with vaccination.

Hepatitis B virus (HBV) carriers with lymphoid malignancies have a high risk of HBV reactivation and disease,[223] especially for patients treated with anti-CD20 monoclonal antibodies (e.g., rituximab, ofatumumab).[224,225] Management recommendations for prevention of HBV reactivation (including surveillance and antiviral prophylaxis or pre-emptive therapy) are discussed in the NHL Guidelines section for overall Supportive Care.

Cytomegalovirus (CMV) reactivation is a well-documented infectious event in patients receiving treatment with alemtuzumab, occurring in up to 25% of patients.[98,99,128,131,134,136] Although the standard approach to CMV monitoring and management remains under debate, current practices include the use of prophylactic ganciclovir (oral or IV) if CMV viremia is present prior to alemtuzumab therapy,[226] or preemptive use of these drugs when the viral load is found to be increasing during therapy.[227,228]

Clinicians should be aware of the high risk of CMV reactivation in patients with CLL treated with alemtuzumab-containing regimens. Monitoring for the presence of CMV antigens regularly using quantitative polymerase chain reaction (PCR) assays is an effective approach to the management of CMV reactivation.[229] The NCCN Guidelines recommend routine surveillance for CMV viremia (every 2–3 weeks) during the treatment course with alemtuzumab and for 2 months following completion of treatment. Consultation with an infectious disease expert may be necessary.

Autoimmune Cytopenias

Autoimmune hemolytic anemia (AIHA), immune-mediated thrombocytopenia, also known as immune thrombocytopenic purpura (ITP) and pure red blood cell aplasia (PRCA) are the most frequent autoimmune cytopenias in patients with CLL.[230,231]

AIHA is the most common form of autoimmune cytopenia. Although direct antiglobulin test (DAT) has been used for the diagnosis of AIHA, most patients with AIHA have negative DAT; additional markers such as low haptoglobin and elevated reticulocyte and LDH are required to confirm the diagnosis of AIHA.[232] Patients with advanced disease, unmutated *IGHV*, increased serum beta-2 microglobulin level, and high expression of ZAP-70 are also at a higher risk of developing AIHA.[232-235]

ITP in patients with CLL is associated with poorer survival independent of common clinical prognostic variables.[236] In a recent Italian study, high WBC count, unmutated *IGHV*, positive DAT and ZAP-70 positivity were associated with the development of ITP in patients with CLL.[236] PRCA is less common in patients with CLL.

Bone marrow evaluation is recommended to confirm the diagnosis of autoimmune cytopenias. Evaluation of parvovirus B19 is also recommended to exclude parvovirus-induced PRCA. AIHA and ITP can be managed with corticosteroids in most cases. IVIG, cyclosporin[237] and splenectomy should be used in steroid-refractory cases. Rituximab has also been effective for the treatment of patients with autoimmune cytopenias [238-244] Corticosteroids tend to be less effective in PRCA than in ITP or AIHA. In the very refractory cases, allogeneic HSCT may be necessary. More recently, synthetic thrombopoietin-like agents such as romiplostim and eltrombopag have shown promising results in the treatment of thrombocytopenia associated with ITP.[245-248] Both romiplostim and eltrombopag are FDA-approval for the treatment of thrombocytopenia in patients with ITP that is refractory to steroids, IVIG and splenectomy.

Purine analog-based therapy has been associated with AIHA. Recent studies have reported higher incidence of AIHA in patients treated with fludarabine or chlorambucil compared to those who received fludarabine-based combination regimens (FC or FCR).[232,249] AIHA should not preclude the use of combination therapy containing fludarabine, and patients should be observed carefully. In the case of severe AIHA, fludarabine therapy should be discontinued and subsequent use of the agent should be avoided.

Tumor Flare Reactions

Tumor flare reactions were commonly reported in patients with CLL treated with lenalidomide. In phase II studies of single-agent lenalidomide in relapsed/refractory CLL, tumor flare occurred in approximately 30% to 60% of patients.[106,142] A higher incidence (approximately 50–90%) was reported in the first-line setting, although these reactions were limited to grade 1 or 2 events.[110,112] Tumor flare reaction is typically observed as painful enlargement of lymph nodes, and may be accompanied by spleen enlargement, low-grade fever, rash, and/or bone pain. Tumor flare was more frequent among patients with enlarged (>5 cm) lymph nodes at baseline.[106] For patients who experience tumor flare reactions while treated with lenalidomide-containing regimens, the panel recommends the use of steroids to manage lymph node enlargement and inflammation, and antihistamines to manage rash/pruritus. For patients with bulky (> 5 cm) lymph nodes prior to start of therapy, tumor flare prophylaxis with steroids may be considered for the first 10 to 14 days of therapy. Severe tumor flare reaction is generally rare if an anti-CD20 monoclonal antibody is initiated at least 1 week prior to start of lenalidomide for those patients treated with the combination regimen.

Venous Thromboembolism

Lenalidomide has been associated with increased risks for venous thromboembolism (deep vein thrombosis or pulmonary embolism) in patients with myelodysplastic syndromes or multiple myeloma, particularly when combined with dexamethasone or with chemotherapy agents.[250-255] Published guidelines recommend that patients with multiple myeloma treated with lenalidomide- or thalidomide-containing combination regimens receive prophylactic anticoagulation with low-molecular weight heparin or warfarin to prevent venous thromboembolism.[253] Treatment with lenalidomide may also be associated with venous thromboembolic events in patients with

CLL,[106,142,256] but routine prophylactic anticoagulation is currently not indicated. Prophylaxis with daily low-dose aspirin (81 mg daily) may be considered in patients with extremely high platelet counts at baseline.

Tumor Lysis Syndrome

Patients with CLL and high white blood cell counts may occasionally experience tumor lysis syndrome and should be managed as outlined under "Tumor Lysis Syndrome" in the "Supportive Care" section of the Guidelines.

References

1. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 1997;89:3909-3918. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9166827.

2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63:11-30. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23335087.

3. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008;111:5446-5456. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18216293.

4. Tsimberidou AM, Wen S, O'Brien S, et al. Assessment of chronic lymphocytic leukemia and small lymphocytic lymphoma by absolute lymphocyte counts in 2,126 patients: 20 years of experience at the University of Texas M.D. Anderson Cancer Center. J Clin Oncol 2007;25:4648-4656. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17925562.

5. Rawstron AC. Monoclonal B-cell lymphocytosis. Hematology Am Soc Hematol Educ Program 2009:430-439. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20008229.

6. Rawstron AC, Bennett FL, O'Connor SJ, et al. Monoclonal B-cell lymphocytosis and chronic lymphocytic leukemia. N Engl J Med 2008;359:575-583. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18687638.

7. Dicker F, Schnittger S, Haferlach T, et al. Immunostimulatory oligonucleotide-induced metaphase cytogenetics detect chromosomal aberrations in 80% of CLL patients: A study of 132 CLL cases with correlation to FISH, IgVH status, and CD38 expression. Blood 2006;108:3152-3160. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16840733.

8. Put N, Konings P, Rack K, et al. Improved detection of chromosomal abnormalities in chronic lymphocytic leukemia by conventional cytogenetics using CpG oligonucleotide and interleukin-2 stimulation: A Belgian multicentric study. Genes Chromosomes Cancer 2009;48:843-853. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19582829.

9. Struski S, Gervais C, Helias C, et al. Stimulation of B-cell lymphoproliferations with CpG-oligonucleotide DSP30 plus IL-2 is more effective than with TPA to detect clonal abnormalities. Leukemia 2009;23:617-619. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18830262.

10. Heerema NA, Byrd JC, Dal Cin PS, et al. Stimulation of chronic lymphocytic leukemia cells with CpG oligodeoxynucleotide gives consistent karyotypic results among laboratories: a CLL Research Consortium (CRC) Study. Cancer Genet Cytogenet 2010;203:134-140. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21156225.

11. Crespo M, Bosch F, Villamor N, et al. ZAP-70 expression as a surrogate for immunoglobulin-variable-region mutations in chronic lymphocytic leukemia. N Engl J Med 2003;348:1764-1775. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12724482.

12. Damle RN, Wasil T, Fais F, et al. Ig V gene mutation status and CD38 expression as novel prognostic indicators in chronic lymphocytic leukemia. Blood 1999;94:1840-1847. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10477712.

13. Del Poeta G, Maurillo L, Venditti A, et al. Clinical significance of CD38 expression in chronic lymphocytic leukemia. Blood 2001;98:2633-2639. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11675331.

14. Dohner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med

2000;343:1910-1916. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/11136261.

15. Hallek M, Langenmayer I, Nerl C, et al. Elevated serum thymidine kinase levels identify a subgroup at high risk of disease progression in early, nonsmoldering chronic lymphocytic leukemia. Blood 1999;93:1732-1737. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/10029603.

16. Hallek M, Wanders L, Ostwald M, et al. Serum beta(2)-microglobulin and serum thymidine kinase are independent predictors of progression-free survival in chronic lymphocytic leukemia and immunocytoma. Leuk Lymphoma 1996;22:439-447. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/8882957.

17. Hamblin TJ, Davis Z, Gardiner A, et al. Unmutated Ig V(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia. Blood 1999;94:1848-1854. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/10477713.

18. Hamblin TJ, Orchard JA, Ibbotson RE, et al. CD38 expression and immunoglobulin variable region mutations are independent prognostic variables in chronic lymphocytic leukemia, but CD38 expression may vary during the course of the disease. Blood 2002;99:1023-1029. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11807008.

19. Ibrahim S, Keating M, Do KA, et al. CD38 expression as an important prognostic factor in B-cell chronic lymphocytic leukemia. Blood 2001;98:181-186. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/11418478.

20. Orchard JA, Ibbotson RE, Davis Z, et al. ZAP-70 expression and prognosis in chronic lymphocytic leukaemia. Lancet 2004;363:105-111. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14726163.

21. Rassenti LZ, Huynh L, Toy TL, et al. ZAP-70 compared with immunoglobulin heavy-chain gene mutation status as a predictor of disease progression in chronic lymphocytic leukemia. N Engl J Med 2004;351:893-901. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/15329427.

22. Wiestner A, Rosenwald A, Barry TS, et al. ZAP-70 expression identifies a chronic lymphocytic leukemia subtype with unmutated immunoglobulin genes, inferior clinical outcome, and distinct gene expression profile. Blood 2003;101:4944-4951. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/12595313.

23. Tobin G, Thunberg U, Johnson A, et al. Somatically mutated Ig V(H)3-21 genes characterize a new subset of chronic lymphocytic leukemia. Blood 2002;99:2262-2264. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/11877310.

24. Krober A, Bloehdorn J, Hafner S, et al. Additional genetic high-risk features such as 11q deletion, 17p deletion, and V3-21 usage characterize discordance of ZAP-70 and VH mutation status in chronic lymphocytic leukemia. J Clin Oncol 2006;24:969-975. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/16418492.

25. Krober A, Seiler T, Benner A, et al. V(H) mutation status, CD38 expression level, genomic aberrations, and survival in chronic lymphocytic leukemia. Blood 2002;100:1410-1416. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/12149225.

26. Oscier D, Wade R, Davis Z, et al. Prognostic factors identified three risk groups in the LRF CLL4 trial, independent of treatment allocation. Haematologica 2010;95:1705-1712. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/20511662.

27. Oscier DG, Gardiner AC, Mould SJ, et al. Multivariate analysis of prognostic factors in CLL: clinical stage, IGVH gene mutational status, and loss or mutation of the p53 gene are independent prognostic factors. Blood 2002;100:1177-1184. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/12149195.

28. Gentile M, Mauro FR, Calabrese E, et al. The prognostic value of CD38 expression in chronic lymphocytic leukaemia patients studied

prospectively at diagnosis: a single institute experience. Br J Haematol 2005;130:549-557. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16098069.

29. Del Principe MI, Del Poeta G, Buccisano F, et al. Clinical significance of ZAP-70 protein expression in B-cell chronic lymphocytic leukemia. Blood 2006;108:853-861. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16601244.

30. Rassenti LZ, Jain S, Keating MJ, et al. Relative value of ZAP-70, CD38, and immunoglobulin mutation status in predicting aggressive disease in chronic lymphocytic leukemia. Blood 2008;112:1923-1930. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18577710.

31. Tam CS, O'Brien S, Wierda W, et al. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. Blood 2008;112:975-980. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18411418.

32. Tsimberidou AM, Tam C, Wierda W, et al. Beta-2 microglobulin (B2M) is an independent prognostic factor for clinical outcomes in patients with CLL treated with frontline fludarabine, cyclophosphamide, and rituximab (FCR) regardless of age, creatinine clearance (CrCl) [abstract]. J Clin Oncol 2007;25:Abstract 7034. Available at: http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/7034.

33. Wierda WG, O'Brien S, Wang X, et al. Characteristics associated with important clinical end points in patients with chronic lymphocytic leukemia at initial treatment. J Clin Oncol 2009;27:1637-1643. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19224852.

34. Wierda WG, O'Brien S, Wang X, et al. Prognostic nomogram and index for overall survival in previously untreated patients with chronic lymphocytic leukemia. Blood 2007;109:4679-4685. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17299097.

35. Molica S, Mauro FR, Callea V, et al. The utility of a prognostic index for predicting time to first treatment in early chronic lymphocytic

leukemia: the GIMEMA experience. Haematologica 2010;95:464-469. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19903673.

36. Shanafelt TD, Jenkins G, Call TG, et al. Validation of a new prognostic index for patients with chronic lymphocytic leukemia. Cancer 2009;115:363-372. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19090008.

37. Neilson JR, Auer R, White D, et al. Deletions at 11q identify a subset of patients with typical CLL who show consistent disease progression and reduced survival. Leukemia 1997;11:1929-1932. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9369428.

38. Austen B, Skowronska A, Baker C, et al. Mutation status of the residual ATM allele is an important determinant of the cellular response to chemotherapy and survival in patients with chronic lymphocytic leukemia containing an 11q deletion. J Clin Oncol 2007;25:5448-5457. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17968022.

39. Tsimberidou AM, Tam C, Abruzzo LV, et al. Chemoimmunotherapy may overcome the adverse prognostic significance of 11q deletion in previously untreated patients with chronic lymphocytic leukemia. Cancer 2009;115:373-380. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19117034.

40. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet 2010;376:1164-1174. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20888994.

41. Catovsky D, Richards S, Matutes E, et al. Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukaemia (the LRF CLL4 Trial): a randomised controlled trial. Lancet 2007;370:230-239. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17658394.

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42. Stilgenbauer S, Sander S, Bullinger L, et al. Clonal evolution in chronic lymphocytic leukemia: acquisition of high-risk genomic aberrations associated with unmutated VH, resistance to therapy, and short survival. Haematologica 2007;92:1242-1245. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17666364.

43. Wierda WG, O'Brien S, Wang X, et al. Multivariable model for time to first treatment in patients with chronic lymphocytic leukemia. J Clin Oncol 2011;29:4088-4095. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21969505.

44. Zenz T, Eichhorst B, Busch R, et al. TP53 Mutation and Survival in Chronic Lymphocytic Leukemia. Journal of Clinical Oncology 2010;28:4473-4479. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20697090.

45. Zenz T, Hoth P, Busch R, et al. TP53 mutations and outcome after fludarabine and cyclophosphamide (FC) or FC plus rituximab (FCR) in the CLL8 trial of the GCLLSG [abstract]. Blood 2009;114:Abstract 1267. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/114/22/1267.

46. Gonzalez D, Martinez P, Wade R, et al. Mutational status of the TP53 gene as a predictor of response and survival in patients with chronic lymphocytic leukemia: results from the LRF CLL4 trial. J Clin Oncol 2011;29:2223-2229. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21483000.

47. Rossi D, Cerri M, Deambrogi C, et al. The prognostic value of TP53 mutations in chronic lymphocytic leukemia is independent of Del17p13: implications for overall survival and chemorefractoriness. Clin Cancer Res 2009;15:995-1004. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19188171.

48. Zenz T, Mohr J, Edelmann J, et al. Treatment resistance in chronic lymphocytic leukemia: the role of the p53 pathway. Leuk Lymphoma 2009;50:510-513. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19347737.

49. Woyach JA, Ruppert AS, Heerema NA, et al. Chemoimmunotherapy With Fludarabine and Rituximab Produces Extended Overall Survival and Progression-Free Survival in Chronic Lymphocytic Leukemia: Long-Term Follow-Up of CALGB Study 9712. J Clin Oncol 2011;29:1349-1355. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21321292.

50. Oscier DG, Rose-Zerilli MJ, Winkelmann N, et al. The clinical significance of NOTCH1 and SF3B1 mutations in the UK LRF CLL4 trial. Blood 2013;121:468-475. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23086750.

51. Rossi D, Rasi S, Fabbri G, et al. Mutations of NOTCH1 are an independent predictor of survival in chronic lymphocytic leukemia. Blood 2012;119:521-529. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22077063.

52. Wang L, Lawrence MS, Wan Y, et al. SF3B1 and other novel cancer genes in chronic lymphocytic leukemia. N Engl J Med 2011;365:2497-2506. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22150006.

53. Quesada V, Conde L, Villamor N, et al. Exome sequencing identifies recurrent mutations of the splicing factor SF3B1 gene in chronic lymphocytic leukemia. Nat Genet 2012;44:47-52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22158541.

54. Rossi D, Bruscaggin A, Spina V, et al. Mutations of the SF3B1 splicing factor in chronic lymphocytic leukemia: association with progression and fludarabine-refractoriness. Blood 2011;118:6904-6908. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22039264.

55. Rossi D, Rasi S, Spina V, et al. Different impact of NOTCH1 and SF3B1 mutations on the risk of chronic lymphocytic leukemia transformation to Richter syndrome. Br J Haematol 2012;158:426-429. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22571487.

56. Schnaiter A, Paschka P, Rossi M, et al. NOTCH1, SF3B1, and TP53 mutations in fludarabine-refractory CLL patients treated with alemtuzumab: results from the CLL2H trial of the GCLLSG. Blood

2013;122:1266-1270. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/23821658.

57. Rossi D, Fangazio M, Rasi S, et al. Disruption of BIRC3 associates with fludarabine chemorefractoriness in TP53 wild-type chronic lymphocytic leukemia. Blood 2012;119:2854-2862. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22308293.

58. Rossi D, Rasi S, Spina V, et al. Integrated mutational and cytogenetic analysis identifies new prognostic subgroups in chronic lymphocytic leukemia. Blood 2013. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23243274.

59. Rai KR, Sawitsky A, Cronkite EP, et al. Clinical staging of chronic lymphocytic leukemia. Blood 1975;46:219-234. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1139039.

60. Binet J, Auquier A, Dighiero G, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer 1981;48:198-206. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7237385.

61. Cheson BD, Bennett JM, Grever M, et al. National Cancer Institute-sponsored Working Group guidelines for chronic lymphocytic leukemia: revised guidelines for diagnosis and treatment. Blood 1996;87:4990-4997. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8652811.

62. Raphael B, Andersen JW, Silber R, et al. Comparison of chlorambucil and prednisone versus cyclophosphamide, vincristine, and prednisone as initial treatment for chronic lymphocytic leukemia: long-term follow-up of an Eastern Cooperative Oncology Group randomized clinical trial. J Clin Oncol 1991;9:770-776. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2016618.

63. Rai KR, Peterson BL, Appelbaum FR, et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. N Engl J Med 2000;343:1750-1757. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11114313.

64. Leporrier M, Chevret S, Cazin B, et al. Randomized comparison of fludarabine, CAP, and ChOP in 938 previously untreated stage B and C chronic lymphocytic leukemia patients. Blood 2001;98:2319-2325. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11588025.

65. National Cancer Institute. SEER Stat Fact Sheets: Chronic Lymphocytic Leukemia. Bethesda, MD: 2012. Available at: http://seer.cancer.gov/statfacts/html/clyl.html. Accessed August 2012.

66. Eichhorst B, Goede V, Hallek M. Treatment of elderly patients with chronic lymphocytic leukemia. Leuk Lymphoma 2009;50:171-178. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19197731.

67. Eichhorst BF, Busch R, Stilgenbauer S, et al. First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. Blood 2009;114:3382-3391. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19605849.

68. Hainsworth JD, Litchy S, Barton JH, et al. Single-agent rituximab as first-line and maintenance treatment for patients with chronic lymphocytic leukemia or small lymphocytic lymphoma: a phase II trial of the Minnie Pearl Cancer Research Network. J Clin Oncol 2003;21:1746-1751. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12721250.

69. Castro JE, James DF, Sandoval-Sus JD, et al. Rituximab in combination with high-dose methylprednisolone for the treatment of chronic lymphocytic leukemia. Leukemia 2009;23:1779-1789. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19693094.

70. Foa R, Alietti A, Guarini A, et al. A phase II study of chlorambucil rituximab (CLB-R) followed by R maintenance vs observation in elderly patients with previously untreated chronic lymphocytic leukemia (CLL): Induction phase results [abstract]. Haematologica 2011;96 (Supple 2):Abstract 532. Available at:

71. Hillmen P, Gribben JG, Follows GA, et al. Rituximab plus chlorambucil (R-Chlorambucil) as first-line treatment for chronic

lymphocytic leukaemia (CLL): Final analysis of an open-label phase II study [abstract] Ann Oncol 2011;22 (Suppl 4):Abstract 120. Available at: http://annonc.oxfordjournals.org/content/22/suppl_4/iv123.full.pdf+html.

72. Mossner E, Brunker P, Moser S, et al. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. Blood 2010;115:4393-4402. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20194898.

73. Herter S, Herting F, Mundigl O, et al. Preclinical Activity of the Type II CD20 Antibody GA101 (Obinutuzumab) Compared with Rituximab and Ofatumumab In Vitro and in Xenograft Models. Mol Cancer Ther 2013. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23873847.

74. Bologna L, Gotti E, Manganini M, et al. Mechanism of action of type II, glycoengineered, anti-CD20 monoclonal antibody GA101 in B-chronic lymphocytic leukemia whole blood assays in comparison with rituximab and alemtuzumab. J Immunol 2011;186:3762-3769. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21296976.

75. Rafiq S, Butchar JP, Cheney C, et al. Comparative assessment of clinically utilized CD20-directed antibodies in chronic lymphocytic leukemia cells reveals divergent NK cell, monocyte, and macrophage properties. J Immunol 2013;190:2702-2711. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23418626.

76. Cartron G, Morschhauser F, Thieblemont C, et al. Results from a phase II study of obinutuzumab (GA101) monotherapy in relapsed/refractory chronic lymphocytic leukemia (CLL) [abstract]. Haematologica 2011;96 (Suppl 2). Available at: http://www.haematologica.org/content/96/supplement_2/1.full.pdf+html.

77. Goede V, Fischer K, Humphrey K, et al. Obinutuzumab (GA101) plus chlorambucil (Clb) or rituximab (R) plus Clb versus Clb alone in patients with chronic lymphocytic leukemia (CLL) and preexisting medical conditions (comorbidities): Final stage 1 results of the CLL11

(BO21004) phase III trial. ASCO Meeting Abstracts 2013;31:7004. Available at: http://meeting.ascopubs.org/cgi/content/abstract/31/15_suppl/7004.

78. Salles G, Morschhauser F, Lamy T, et al. Phase 1 study results of the type II glycoengineered humanized anti-CD20 monoclonal antibody obinutuzumab (GA101) in B-cell lymphoma patients. Blood 2012;119:5126-5132. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22431570.

79. Sehn LH, Assouline SE, Stewart DA, et al. A phase 1 study of obinutuzumab induction followed by 2 years of maintenance in patients with relapsed CD20-positive B-cell malignancies. Blood 2012;119:5118-5125. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22438256.

80. Eichhorst BF, Busch R, Hopfinger G, et al. Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukemia. Blood 2006;107:885-891. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16219797.

81. Flinn IW, Neuberg DS, Grever MR, et al. Phase III trial of fludarabine plus cyclophosphamide compared with fludarabine for patients with previously untreated chronic lymphocytic leukemia: US Intergroup Trial E2997. J Clin Oncol 2007;25:793-798. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17283364.

82. Byrd JC, Peterson BL, Morrison VA, et al. Randomized phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukemia: results from Cancer and Leukemia Group B 9712 (CALGB 9712). Blood 2003;101:6-14. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12393429.

83. Byrd JC, Rai K, Peterson BL, et al. Addition of rituximab to fludarabine may prolong progression-free survival and overall survival in patients with previously untreated chronic lymphocytic leukemia: an updated retrospective comparative analysis of CALGB 9712 and

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CALGB 9011. Blood 2005;105:49-53. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/15138165.

84. Keating MJ, O'Brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. J Clin Oncol 2005;23:4079-4088. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/15767648.

85. Parikh SA, Wierda WG, Badoux X, et al. Comparison of fludarabine (F) plus cyclophosphamide (C) versus FC plus rituximab (R) in previously untreated Rai stage III/IV chronic lymphocytic leukemia (CLL). J Clin Oncol 2010;28:Abstract 6519. Available at:
http://meeting.ascopubs.org/cgi/content/abstract/28/15_suppl/6519.

86. Kay NE, Geyer SM, Call TG, et al. Combination chemoimmunotherapy with pentostatin, cyclophosphamide, and rituximab shows significant clinical activity with low accompanying toxicity in previously untreated B chronic lymphocytic leukemia. Blood 2007;109:405-411. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/17008537.

87. Reynolds C, Di Bella N, Lyons RM, et al. Phase III trial of fludarabine, cyclophosphamide, and rituximab vs. pentostatin, cyclophosphamide, and rituximab in B-cell chronic lymphocytic leukemia [abstract]. Blood 2008;112:Abstract 327. Available at:
http://abstracts.hematologylibrary.org/cgi/content/abstract/112/11/327.

88. Kay NE, Wu W, Kabat B, et al. Pentostatin and rituximab therapy for previously untreated patients with B-cell chronic lymphocytic leukemia. Cancer 2010;116:2180-2187. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/20187101.

89. Leoni LM, Bailey B, Reifert J, et al. Bendamustine (Treanda) displays a distinct pattern of cytotoxicity and unique mechanistic features compared with other alkylating agents. Clin Cancer Res 2008;14:309-317. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/18172283.

90. Strumberg D, Harstrick A, Doll K, et al. Bendamustine hydrochloride activity against doxorubicin-resistant human breast carcinoma cell lines. Anticancer Drugs 1996;7:415-421. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/8826610.

91. Knauf WU, Lissichkov T, Aldaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol 2009;27:4378-4384. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/19652068.

92. Knauf WU, Lissitchkov T, Aldaoud A, et al. Bendamustine induces higher remission rates, prolongs progression free survival as well as time to next treatment, and improves overall survival for patients in complete remission without compromising quality of life when compared to chlorambucil in first line treatment of chronic lymphocytic leukemia. Blood 2010;116:2449. Available at:
http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/2449.

93. Knauf WU, Lissitchkov T, Aldaoud A, et al. Bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukaemia: updated results of a randomized phase III trial. Br J Haematol 2012;159:67-77. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/22861163.

94. Knauf WU, Lissitchkov T, Aldaoud A, et al. Bendamustine in the Treatment of Chronic Lymphocytic Leukemia -Consistent Superiority Over Chlorambucil in Elderly Patients and Across Clinically Defined Risk Groups [abstract]. Blood 2009;114:Abstract 2367. Available at:
http://abstracts.hematologylibrary.org/cgi/content/abstract/114/22/2367.

95. Fischer K, Cramer P, Busch R, et al. Bendamustine in Combination With Rituximab for Previously Untreated Patients With Chronic Lymphocytic Leukemia: A Multicenter Phase II Trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol 2012;30:3209-3216. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/22869884.

96. Fischer K, Cramer P, Stilgenbauer S, et al. Bendamustine combined with rituximab (BR) in first-line therapy of advanced CLL: a multicenter phase II trial of the German CLL Study Group (GCLLSG) [abstract]. Blood 2009;114:Abstract 205. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/114/22/205.

97. Leblond V, Laribi K, Ilhan O, et al. Rituximab in Combination with Bendamustine or Chlorambucil for Treating Patients with Chronic Lymphocytic Leukemia: Interim Results of a Phase IIIb Study (MaBLe) [abstract]. Blood 2012;120:Abstract 2744. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/120/21/2744.

98. Lundin J, Kimby E, Bjorkholm M, et al. Phase II trial of subcutaneous anti-CD52 monoclonal antibody alemtuzumab (Campath-1H) as first-line treatment for patients with B-cell chronic lymphocytic leukemia (B-CLL). Blood 2002;100:768-773. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12130484.

99. Hillmen P, Skotnicki AB, Robak T, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. J Clin Oncol 2007;25:5616-5623. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17984186.

100. Lozanski G, Heerema NA, Flinn IW, et al. Alemtuzumab is an effective therapy for chronic lymphocytic leukemia with p53 mutations and deletions. Blood 2004;103:3278-3281. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14726385.

101. Osuji NC, Del Giudice I, Matutes E, et al. The efficacy of alemtuzumab for refractory chronic lymphocytic leukemia in relation to cytogenetic abnormalities of p53. Haematologica 2005;90:1435-1436. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16219582.

102. Stilgenbauer S, Dohner H. Campath-1H-induced complete remission of chronic lymphocytic leukemia despite p53 gene mutation and resistance to chemotherapy. N Engl J Med 2002;347:452-453. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12167696.

103. Zenz T, Habe S, Denzel T, et al. Detailed analysis of p53 pathway defects in fludarabine-refractory chronic lymphocytic leukemia (CLL): dissecting the contribution of 17p deletion, TP53 mutation, p53-p21 dysfunction, and miR34a in a prospective clinical trial. Blood 2009;114:2589-2597. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19643983.

104. Andritsos LA, Johnson AJ, Lozanski G, et al. Higher doses of lenalidomide are associated with unacceptable toxicity including life-threatening tumor flare in patients with chronic lymphocytic leukemia. J Clin Oncol 2008;26:2519-2525. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18427150.

105. Corral LG, Haslett PA, Muller GW, et al. Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha. J Immunol 1999;163:380-386. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10384139.

106. Ferrajoli A, Lee BN, Schlette EJ, et al. Lenalidomide induces complete and partial remissions in patients with relapsed and refractory chronic lymphocytic leukemia. Blood 2008;111:5291-5297. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18334676.

107. LeBlanc R, Hideshima T, Catley LP, et al. Immunomodulatory drug costimulates T cells via the B7-CD28 pathway. Blood 2004;103:1787-1790. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14512311.

108. Reddy N, Hernandez-Ilizaliturri FJ, Deeb G, et al. Immunomodulatory drugs stimulate natural killer-cell function, alter cytokine production by dendritic cells, and inhibit angiogenesis enhancing the anti-tumour activity of rituximab in vivo. Br J Haematol 2008;140:36-45. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17995965.

109. Wu L, Adams M, Carter T, et al. lenalidomide enhances natural killer cell and monocyte-mediated antibody-dependent cellular cytotoxicity of rituximab-treated CD20+ tumor cells. Clin Cancer Res

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2008;14:4650-4657. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18628480.

110. Chen CI, Bergsagel PL, Paul H, et al. Single-agent lenalidomide in the treatment of previously untreated chronic lymphocytic leukemia. J Clin Oncol 2011;29:1175-1181. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21189385.

111. Chen C, Paul H, Wang T, et al. Long-Term Follow-up of a Phase 2 Study of Single Agent Lenalidomide in Previously Untreated, Symptomatic Chronic Lymphocytic Leukemia (CLL) [abstract]. Blood 2012;120:Abstract 718. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/120/21/718.

112. Badoux XC, Keating MJ, Wen S, et al. Lenalidomide as initial therapy of elderly patients with chronic lymphocytic leukemia. Blood 2011;118:3489-3498. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21725050.

113. Strati P, Keating MJ, Wierda WG, et al. Lenalidomide induces long-lasting responses in elderly patients with chronic lymphocytic leukemia. Blood 2013;122:734-737. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23801633.

114. James DF, Brown JR, Werner L, et al. Lenalidomide and Rituximab for the Initial Treatment of Patients with Chronic Lymphocytic Leukemia (CLL) A Multicenter Study of the CLL Research Consortium [abstract]. Blood 2011;118:Abstract 291. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/118/21/291.

115. U.S. Food and Drug Administration. FDA Statement: FDA halts clinical trial of drug Revlimid (lenalidomide) for chronic lymphocytic leukemia due to safety concerns. 2013. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm361444.htm. Accessed July 2013

116. Wierda W, O'Brien S, Wen S, et al. Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab for relapsed and refractory chronic lymphocytic leukemia. J Clin Oncol 2005;23:4070-4078. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15767647.

117. Badoux XC, Keating MJ, Wang X, et al. Fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy is highly effective treatment for relapsed patients with CLL. Blood 2011;117:3016-3024. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21245487.

118. Robak T, Dmoszynska A, Solal-Celigny P, et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. J Clin Oncol 2010;28:1756-1765. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20194844.

119. Lamanna N, Kalaycio M, Maslak P, et al. Pentostatin, cyclophosphamide, and rituximab is an active, well-tolerated regimen for patients with previously treated chronic lymphocytic leukemia. J Clin Oncol 2006;24:1575-1581. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16520464.

120. Weiss MA, Maslak PG, Jurcic JG, et al. Pentostatin and cyclophosphamide: an effective new regimen in previously treated patients with chronic lymphocytic leukemia. J Clin Oncol 2003;21:1278-1284. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12663715.

121. Tsimberidou AM, Wierda WG, Plunkett W, et al. Phase I-II study of oxaliplatin, fludarabine, cytarabine, and rituximab combination therapy in patients with Richter's syndrome or fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol 2008;26:196-203. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18182662.

122. Tsimberidou AM, Wierda WG, Wen S, et al. Results of a phase I-II clinical trial of oxaliplatin, fludarabine, cytarabine, and rituximab (OFAR) combination therapy in patients with aggressive, relapsed/refractory chronic lymphocytic leukemia (CLL) and Richter syndrome (RS). Blood 2010;116:923. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/923.

123. Fischer K, Stilgenbauer S, Schweighofer CD, et al. Bendamustine in combination with rituximab (BR) for patients with relapsed chronic lymphocytic leukemia (CLL): a multicentre phase II trial of the German CLL Study Group (GCLLSG) [abstract 330]. Blood 2008;112:Abstract 330. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/112/11/330.

124. Fischer K, Cramer P, Busch R, et al. Bendamustine Combined With Rituximab in Patients With Relapsed and/or Refractory Chronic Lymphocytic Leukemia: A Multicenter Phase II Trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol 2011:3559-3566. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21844497.

125. Bowen DA, Call TG, Jenkins GD, et al. Methylprednisolone-rituximab is an effective salvage therapy for patients with relapsed chronic lymphocytic leukemia including those with unfavorable cytogenetic features. Leuk Lymphoma 2007;48:2412-2417. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18067017.

126. Castro JE, Sandoval-Sus JD, Bole J, et al. Rituximab in combination with high-dose methylprednisolone for the treatment of fludarabine refractory high-risk chronic lymphocytic leukemia. Leukemia 2008;22:2048-2053. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18754025.

127. Dungarwalla M, Evans SO, Riley U, et al. High dose methylprednisolone and rituximab is an effective therapy in advanced refractory chronic lymphocytic leukemia resistant to fludarabine therapy. Haematologica 2008;93:475-476. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18310545.

128. Keating MJ, Flinn I, Jain V, et al. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study. Blood 2002;99:3554-3561. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11986207.

129. Varghese AM, Sayala HA, Moreton P, et al. Long term survival report of the UKCLL02 trial: a phase II study of subcutaneous alemtuzumab in patients with fludarabine refractory CLL (on behalf of the NCRI CLL trials sub-group). Blood 2010;116:922. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/922.

130. Fiegl M, Erdel M, Tinhofer I, et al. Clinical outcome of pretreated B-cell chronic lymphocytic leukemia following alemtuzumab therapy: a retrospective study on various cytogenetic risk categories. Annals of Oncology 2010;21:2410-2419. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20466745.

131. Fiegl M, Falkner A, Hopfinger G, et al. Routine clinical use of alemtuzumab in patients with heavily pretreated B-cell chronic lymphocytic leukemia: a nation-wide retrospective study in Austria. Cancer 2006;107:2408-2416. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17054106.

132. Cortelezzi A, Pasquini MC, Sarina B, et al. A pilot study of low-dose subcutaneous alemtuzumab therapy for patients with chemotherapy-refractory chronic lymphocytic leukemia. Haematologica 2005;90:410-412. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15749678.

133. Karlsson C, Lundin J, Kimby E, et al. Phase II study of subcutaneous alemtuzumab without dose escalation in patients with advanced-stage, relapsed chronic lymphocytic leukaemia. Br J Haematol 2009;144:78-85. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19016731.

134. Stilgenbauer S, Zenz T, Winkler D, et al. Subcutaneous alemtuzumab in fludarabine-refractory chronic lymphocytic leukemia: clinical results and prognostic marker analyses from the CLL2H study of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol 2009;27:3994-4001. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19597025.

135. Cortelezzi A, Pasquini MC, Gardellini A, et al. Low-dose subcutaneous alemtuzumab in refractory chronic lymphocytic leukaemia (CLL): results of a prospective, single-arm multicentre study. Leukemia

2009;23:2027-2033. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/19641526.

136. Nguyen DD, Cao TM, Dugan K, et al. Cytomegalovirus viremia during Campath-1H therapy for relapsed and refractory chronic lymphocytic leukemia and prolymphocytic leukemia. Clin Lymphoma 2002;3:105-110. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/12435283.

137. Elter T, Borchmann P, Schulz H, et al. Fludarabine in combination with alemtuzumab is effective and feasible in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: results of a phase II trial. J Clin Oncol 2005;23:7024-7031. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/16145065.

138. Elter T, Gercheva-Kyuchukova L, Pylylpenko H, et al. Fludarabine plus alemtuzumab versus fludarabine alone in patients with previously treated chronic lymphocytic leukaemia: a randomised phase 3 trial. Lancet Oncol 2011;12:1204-1213. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/21992852.

139. Elter T, James R, Stilgenbauer S, et al. Chemoimmuno-Therapy with Fludarabine, Cyclophosphamide and Alemtuzumab (FC-Cam) in Patients with Relapsed or Genetic High-Risk CLL: Final Analysis of the CLL2L Trial of the German CLL Study Group [abstract]. Blood 2009;114:Abstract 209. Available at:
http://abstracts.hematologylibrary.org/cgi/content/abstract/114/22/209.

140. Faderl S, Ferrajoli A, Wierda W, et al. Alemtuzumab by continuous intravenous infusion followed by subcutaneous injection plus rituximab in the treatment of patients with chronic lymphocytic leukemia recurrence. Cancer 2010;116:2360-2365. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/20225334.

141. Badoux XC, Keating MJ, Wang X, et al. Cyclophosphamide, fludarabine, rituximab and alemtuzumab (CFAR) as salvage therapy for heavily pre-treated patients with chronic lymphocytic leukemia. Blood 2011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21670470.

142. Chanan-Khan A, Miller KC, Musial L, et al. Clinical efficacy of lenalidomide in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase II study. J Clin Oncol 2006;24:5343-5349. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17088571.

143. Badoux XC, Keating MJ, O'Brien S, et al. Final Analysis of a Phase 2 Study of Lenalidomide and Rituximab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia (CLL) [abstract]. Blood 2011;118:Abstract 980. Available at:
http://abstracts.hematologylibrary.org/cgi/content/abstract/118/21/980.

144. Badoux XC, Keating MJ, Wen S, et al. Phase II Study of Lenalidomide and Rituximab As Salvage Therapy for Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia. J Clin Oncol 2013;31:584-591. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/23270003.

145. Wierda WG, Kipps TJ, Mayer J, et al. Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol 2010;28:1749-1755. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/20194866.

146. Wierda WG, Kipps TJ, Mayer J, et al. Final analysis from the international trial of single-agent ofatumumab in patients with fludarabine-refractory chronic lymphocytic leukemia [abstract]. Blood 2010;116:Abstract 921. Available at:
http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/921.

147. Gribben JG, Zahrieh D, Stephans K, et al. Autologous and allogeneic stem cell transplantations for poor-risk chronic lymphocytic leukemia. Blood 2005;106:4389-4396. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/16131571.

148. Khouri IF, Keating MJ, Saliba RM, Champlin RE. Long-term follow-up of patients with CLL treated with allogeneic hematopoietic transplantation. Cytotherapy 2002;4:217-221. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/12194718.

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149. Sorror ML, Storer BE, Sandmaier BM, et al. Five-year follow-up of patients with advanced chronic lymphocytic leukemia treated with allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. J Clin Oncol 2008;26:4912-4920. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18794548.

150. Khouri IF, Saliba RM, Admirand J, et al. Graft-versus-leukaemia effect after non-myeloablative haematopoietic transplantation can overcome the unfavourable expression of ZAP-70 in refractory chronic lymphocytic leukaemia. Br J Haematol 2007;137:355-363. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17456058.

151. Moreno C, Villamor N, Colomer D, et al. Allogeneic stem-cell transplantation may overcome the adverse prognosis of unmutated VH gene in patients with chronic lymphocytic leukemia. Journal of Clinical Oncology 2005;23:3433-3438. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15809449.

152. Schetelig J, van Biezen A, Brand R, et al. Allogeneic hematopoietic stem-cell transplantation for chronic lymphocytic leukemia with 17p deletion: a retrospective European Group for Blood and Marrow Transplantation analysis. J Clin Oncol 2008;26:5094-5100. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18711173.

153. Dreger P, Stilgenbauer S, Boettcher S, et al. Prognostic factors for outcome of nonmyeloablative allogeneic stem cell transplantation (NST) in poor-risk chronic lymphocytic leukemia (CLL): final results from a prospective multicenter trial (GCLLSG CLL3X study) [abstract]. Blood 2008;112:Abstract 565. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/112/11/565.

154. Dreger P, Dohner H, Ritgen M, et al. Allogeneic stem cell transplantation provides durable disease control in poor-risk chronic lymphocytic leukemia: long-term clinical and MRD results of the German CLL Study Group CLL3X trial. Blood 2010;116:2438-2447. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20595516.

155. Tsimberidou AM, Keating MJ. Treatment of fludarabine-refractory chronic lymphocytic leukemia. Cancer 2009;115:2824-2836. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19402170.

156. Cramer P, Goede V, Jenke P, et al. Impact of Different Chemotherapy Regimen in Comorbid Patients with Advanced Chronic Lymphocytic Leukemia: Metaanalysis of Two Phase-III-Trials of the German CLL Study Group [abstract]. Blood 2006;108:Abstract 2840. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/108/11/2840.

157. Thurmes P, Call T, Slager S, et al. Comorbid conditions and survival in unselected, newly diagnosed patients with chronic lymphocytic leukemia. Leuk Lymphoma 2008;49:49-56. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18203011.

158. Reyes C, Satram-Hoang S, Hoang K, et al. What Is the Impact of Comorbidity Burden On Treatment Patterns and Outcomes in Elderly Chronic Lymphocytic Leukemia Patients? [abstract]. Blood 2012;120:Abstract 758. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/120/21/758.

159. Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. J Am Geriatr Soc 2008;56:1926-1931. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18811613.

160. Cazin B, Divine M, Lepretre S, et al. High efficacy with five days schedule of oral fludarabine phosphate and cyclophosphamide in patients with previously untreated chronic lymphocytic leukaemia. Br J Haematol 2008;143:54-59. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18710390.

161. Dearden CE, Richards S, Else M, et al. A comparison of the efficacy and safety of oral and intravenous fludarabine in chronic lymphocytic leukemia in the LRF CLL4 trial. Cancer 2010. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21157963.

National Comprehensive Cancer Network®

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162. Rossi JF, van Hoof A, de Boeck K, et al. Efficacy and safety of oral fludarabine phosphate in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol 2004;22:1260-1267. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15051774.

163. Keating MJ, Wierda WG, Tam CS, et al. Long term outcome following treatment failure of FCR chemoimmunotherapy as initial therapy for chronic lymphocytic leukemia [abstract]. Blood 2009;114:Abstract 2381. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/114/22/2381.

164. Rossi D, Gaidano G. Richter syndrome: molecular insights and clinical perspectives. Hematol Oncol 2009;27:1-10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19206112.

165. Tsimberidou AM, Keating MJ. Richter syndrome: biology, incidence, and therapeutic strategies. Cancer 2005;103:216-228. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15578683.

166. Tsimberidou AM, O'Brien S, Kantarjian HM, et al. Hodgkin transformation of chronic lymphocytic leukemia: the M. D. Anderson Cancer Center experience. Cancer 2006;107:1294-1302. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16902984.

167. Tsimberidou AM, O'Brien S, Khouri I, et al. Clinical outcomes and prognostic factors in patients with Richter's syndrome treated with chemotherapy or chemoimmunotherapy with or without stem-cell transplantation. J Clin Oncol 2006;24:2343-2351. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16710033.

168. Cory S, Adams JM. The Bcl2 family: regulators of the cellular life-or-death switch. Nat Rev Cancer 2002;2:647-656. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12209154.

169. Hanada M, Delia D, Aiello A, et al. bcl-2 gene hypomethylation and high-level expression in B-cell chronic lymphocytic leukemia. Blood 1993;82:1820-1828. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8104532.

170. Roberts AW, Seymour JF, Brown JR, et al. Substantial susceptibility of chronic lymphocytic leukemia to BCL2 inhibition: results of a phase I study of navitoclax in patients with relapsed or refractory disease. J Clin Oncol 2012;30:488-496. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22184378.

171. Vogler M, Dinsdale D, Dyer MJ, Cohen GM. ABT-199 selectively inhibits BCL2 but not BCL2L1 and efficiently induces apoptosis of chronic lymphocytic leukaemic cells but not platelets. Br J Haematol 2013. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23826785.

172. Vogler M, Hamali HA, Sun XM, et al. BCL2/BCL-X(L) inhibition induces apoptosis, disrupts cellular calcium homeostasis, and prevents platelet activation. Blood 2011;117:7145-7154. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21562047.

173. Souers AJ, Leverson JD, Boghaert ER, et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. Nat Med 2013;19:202-208. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23291630.

174. Vandenberg CJ, Cory S. ABT-199, a new Bcl-2-specific BH3 mimetic, has in vivo efficacy against aggressive Myc-driven mouse lymphomas without provoking thrombocytopenia. Blood 2013;121:2285-2288. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23341542.

175. Seymour JF, Davids MS, Pagel JM, et al. Updated results of a phase I first-in-human study of the BCL-2 inhibitor ABT-199 (GDC-0199) in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) [abstract]. J Clin Oncol 2013;31:Abstract 7018. Available at: http://meeting.ascopubs.org/cgi/content/abstract/31/15_suppl/7018.

176. Fuentes-Panana EM, Bannish G, Monroe JG. Basal B-cell receptor signaling in B lymphocytes: mechanisms of regulation and role in positive selection, differentiation, and peripheral survival. Immunol Rev 2004;197:26-40. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14962184.

177. Niiro H, Clark EA. Regulation of B-cell fate by antigen-receptor signals. Nat Rev Immunol 2002;2:945-956. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12461567.

178. Buchner M, Baer C, Prinz G, et al. Spleen tyrosine kinase inhibition prevents chemokine- and integrin-mediated stromal protective effects in chronic lymphocytic leukemia. Blood 2010;115:4497-4506. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20335218.

179. Buchner M, Fuchs S, Prinz G, et al. Spleen tyrosine kinase is overexpressed and represents a potential therapeutic target in chronic lymphocytic leukemia. Cancer Res 2009;69:5424-5432. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19549911.

180. Young RM, Hardy IR, Clarke RL, et al. Mouse models of non-Hodgkin lymphoma reveal Syk as an important therapeutic target. Blood 2009;113:2508-2516. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18981293.

181. Okkenhaug K, Vanhaesebroeck B. PI3K in lymphocyte development, differentiation and activation. Nat Rev Immunol 2003;3:317-330. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12669022.

182. Ortolano S, Hwang IY, Han SB, Kehrl JH. Roles for phosphoinositide 3-kinases, Bruton's tyrosine kinase, and Jun kinases in B lymphocyte chemotaxis and homing. Eur J Immunol 2006;36:1285-1295. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16619289.

183. Srinivasan L, Sasaki Y, Calado DP, et al. PI3 kinase signals BCR-dependent mature B cell survival. Cell 2009;139:573-586. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19879843.

184. de Gorter DJ, Beuling EA, Kersseboom R, et al. Bruton's tyrosine kinase and phospholipase Cgamma2 mediate chemokine-controlled B cell migration and homing. Immunity 2007;26:93-104. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17239630.

185. Genevier HC, Hinshelwood S, Gaspar HB, et al. Expression of Bruton's tyrosine kinase protein within the B cell lineage. Eur J Immunol 1994;24:3100-3105. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7805739.

186. Honigberg LA, Smith AM, Sirisawad M, et al. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. Proc Natl Acad Sci U S A 2010;107:13075-13080. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20615965.

187. Spaargaren M, Beuling EA, Rurup ML, et al. The B cell antigen receptor controls integrin activity through Btk and PLCgamma2. J Exp Med 2003;198:1539-1550. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14610042.

188. Quiroga MP, Balakrishnan K, Kurtova AV, et al. B-cell antigen receptor signaling enhances chronic lymphocytic leukemia cell migration and survival: specific targeting with a novel spleen tyrosine kinase inhibitor, R406. Blood 2009;114:1029-1037. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19491390.

189. Baudot AD, Jeandel PY, Mouska X, et al. The tyrosine kinase Syk regulates the survival of chronic lymphocytic leukemia B cells through PKCdelta and proteasome-dependent regulation of Mcl-1 expression. Oncogene 2009;28:3261-3273. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19581935.

190. Chen L, Chen G, Fecteau J-F, et al. Highly Specific Inhibitor for Syk Induces Chronic Lymphocytic Leukemia Cell Apoptosis [abstract]. Blood 2011;118:Abstract 3875. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/118/21/3875.

191. Gobessi S, Laurenti L, Longo PG, et al. Inhibition of constitutive and BCR-induced Syk activation downregulates Mcl-1 and induces apoptosis in chronic lymphocytic leukemia B cells. Leukemia 2009;23:686-697. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19092849.

192. Hoellenriegel J, Coffey GP, Sinha U, et al. Selective, novel spleen tyrosine kinase (Syk) inhibitors suppress chronic lymphocytic leukemia B-cell activation and migration. Leukemia 2012;26:1576-1583. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22362000.

193. Herman SEM, Barr PM, McAuley EM, et al. Fostamatinib Inhibits BCR Signaling, and Reduces Tumor Cell Activation and Proliferation in Patients with Relapsed Refractory Chronic Lymphocytic Leukemia [abstract]. Blood 2012;120:Abstract 2882. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/120/21/2882.

194. Herman SE, Gordon AL, Wagner AJ, et al. Phosphatidylinositol 3-kinase-delta inhibitor CAL-101 shows promising preclinical activity in chronic lymphocytic leukemia by antagonizing intrinsic and extrinsic cellular survival signals. Blood 2010;116:2078-2088. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20522708.

195. Hoellenriegel J, Meadows SA, Sivina M, et al. The phosphoinositide 3'-kinase delta inhibitor, CAL-101, inhibits B-cell receptor signaling and chemokine networks in chronic lymphocytic leukemia. Blood 2011;118:3603-3612. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21803855.

196. Lannutti BJ, Meadows SA, Herman SE, et al. CAL-101, a p110delta selective phosphatidylinositol-3-kinase inhibitor for the treatment of B-cell malignancies, inhibits PI3K signaling and cellular viability. Blood 2011;117:591-594. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20959606.

197. Brown JR, Furman RR, Flinn I, et al. Final results of a phase I study of idelalisib (GSE1101) a selective inhibitor of PI3K{delta}, in patients with relapsed or refractory CLL [abstract]. J Clin Oncol 2013;31:Abstract 7003. Available at: http://meeting.ascopubs.org/cgi/content/abstract/31/15_suppl/7003.

198. Barrientos JC, Furman RR, Leonard J, et al. Update on a phase I study of the selective PI3K{delta} inhibitor idelalisib (GS-1101) in combination with rituximab and/or bendamustine in patients with

relapsed or refractory CLL [abstract]. J Clin Oncol 2013;31:Abstract 7017. Available at: http://meeting.ascopubs.org/cgi/content/abstract/31/15_suppl/7017.

199. O'Brien SM, Lamanna N, Kipps TJ, et al. A phase II study of the selective phosphatidylinositol 3-kinase delta (PI3K{delta}) inhibitor idelalisib (GS-1101) in combination with rituximab (R) in treatment-naive patients (pts) >=65 years with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) [abstract]. J Clin Oncol 2013;31:Abstract 7005. Available at: http://meeting.ascopubs.org/cgi/content/abstract/31/15_suppl/7005.

200. Cheson BD, Byrd JC, Rai KR, et al. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. J Clin Oncol 2012;30:2820-2822. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22778323.

201. Furman RR, Coutre SE, Flinn IE, et al. Update on a phase 1 study of the selective PI3Kd inhibitor, idelalisib (GS-1101) in combination with rituximab, bendamustine, or bendamustine/rituximab in patients with relapsed or refractory chronic lymphocytic leukaemia [abstract]. Hematol Oncol 2013;31 (supple 1):Abstract 298. Available at:

202. de Rooij MF, Kuil A, Geest CR, et al. The clinically active BTK inhibitor PCI-32765 targets B-cell receptor- and chemokine-controlled adhesion and migration in chronic lymphocytic leukemia. Blood 2012;119:2590-2594. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22279054.

203. Herman SE, Gordon AL, Hertlein E, et al. Bruton tyrosine kinase represents a promising therapeutic target for treatment of chronic lymphocytic leukemia and is effectively targeted by PCI-32765. Blood 2011;117:6287-6296. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21422473.

204. Ponader S, Chen SS, Buggy JJ, et al. The Bruton tyrosine kinase inhibitor PCI-32765 thwarts chronic lymphocytic leukemia cell survival

and tissue homing in vitro and in vivo. Blood 2012;119:1182-1189. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22180443.

205. Byrd JC, Furman RR, Coutre S, et al. The Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib (PCI-32765) Promotes High Response Rate, Durable Remissions, and Is Tolerable in Treatment Naive (TN) and Relapsed or Refractory (RR) Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) Patients Including Patients with High-Risk (HR) Disease: New and Updated Results of 116 Patients in a Phase Ib/II Study [abstract]. Blood 2012;120:Abstract 189. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/120/21/189.

206. Advani RH, Buggy JJ, Sharman JP, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. J Clin Oncol 2013;31:88-94. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23045577.

207. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia. N Engl J Med 2013. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23782158.

208. O'Brien SM, Barrientos JC, Flinn IW, et al. Combination of the Bruton's tyrosine kinase (BTK) inhibitor PCI-32765 with bendamustine (B)/rituximab (R) (BR) in patients (pts) with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL): Interim results of a phase Ib/II study [abstract]. J Clin Oncol 2012;30:Abstract 6515. Available at: http://meeting.ascopubs.org/cgi/content/abstract/30/15_suppl/6515.

209. Jaglowski SM, Jones JA, Flynn JM, et al. A phase Ib/II study evaluating activity and tolerability of BTK inhibitor PCI-32765 and ofatumumab in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and related diseases [abstract]. J Clin Oncol 2012;30:Abstract 6508. Available at: http://meeting.ascopubs.org/cgi/content/abstract/30/15_suppl/6508.

210. Herman SEM, Farooqui M, Bezabhie R, et al. In Vivo Effects of Ibrutinib On BCR Signaling, Tumor Cell Activation and Proliferation in Blood and Tissue-Resident Cells of Chronic Lymphocytic Leukemia

Patients [abstract]. Blood 2012;120:Abstract 185. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/120/21/185.

211. Morrison VA. Infectious complications of chronic lymphocytic leukaemia: pathogenesis, spectrum of infection, preventive approaches. Best Pract Res Clin Haematol 2010;23:145-153. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20620978.

212. Tsai HT, Caporaso NE, Kyle RA, et al. Evidence of serum immunoglobulin abnormalities up to 9.8 years before diagnosis of chronic lymphocytic leukemia: a prospective study. Blood 2009;114:4928-4932. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19828698.

213. Perkins JG, Flynn JM, Howard RS, Byrd JC. Frequency and type of serious infections in fludarabine-refractory B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma. Cancer 2002;94:2033-2039. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11932906.

214. Chapel H, Dicato M, Gamm H, et al. Immunoglobulin replacement in patients with chronic lymphocytic leukaemia: a comparison of two dose regimes. Br J Haematol 1994;88:209-212. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7803248.

215. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. A randomized, controlled clinical trial. Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia. N Engl J Med 1988;319:902-907. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2901668.

216. Boughton BJ, Jackson N, Lim S, Smith N. Randomized trial of intravenous immunoglobulin prophylaxis for patients with chronic lymphocytic leukaemia and secondary hypogammaglobulinaemia. Clin Lab Haematol 1995;17:75-80. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7621634.

217. Molica S, Musto P, Chiurazzi F, et al. Prophylaxis against infections with low-dose intravenous immunoglobulins (IVIG) in chronic

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lymphocytic leukemia. Results of a crossover study. Haematologica 1996;81:121-126. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8641639.

218. Raanani P, Gafter-Gvili A, Paul M, et al. Immunoglobulin prophylaxis in chronic lymphocytic leukemia and multiple myeloma: systematic review and meta-analysis. Leukemia & Lymphoma 2009;50:764-772. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19330654.

219. Sinisalo M, Vilpo J, Itala M, et al. Antibody response to 7-valent conjugated pneumococcal vaccine in patients with chronic lymphocytic leukaemia. Vaccine 2007;26:82-87. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18053620.

220. Sinisalo M, Aittoniemi J, Kayhty H, Vilpo J. Vaccination against infections in chronic lymphocytic leukemia. Leuk Lymphoma 2003;44:649-652. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12769342.

221. Van der Velden AM, Van Velzen-Blad H, Claessen AM, et al. The effect of ranitidine on antibody responses to polysaccharide vaccines in patients with B-cell chronic lymphocytic leukaemia. Eur J Haematol 2007;79:47-52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17532765.

222. Jurlander J, de Nully Brown P, Skov PS, et al. Improved vaccination response during ranitidine treatment, and increased plasma histamine concentrations, in patients with B cell chronic lymphocytic leukemia. Leukemia 1995;9:1902-1909. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7475282.

223. Yeo W, Chan PKS, Ho WM, et al. Lamivudine for the prevention of hepatitis B virus reactivation in hepatitis B s-antigen seropositive cancer patients undergoing cytotoxic chemotherapy. J Clin Oncol 2004;22:927-934. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14990649.

224. Biogen Idec, Inc and Genentech, Inc. Prescribing Information. Rituxan (rituximab) Injection for Intravenous Use. 2011. Available at: http://www.gene.com/gene/products/information/pdf/rituxan-prescribing.pdf. Accessed April 2011.

225. GlaxoSmithKline. Prescribing Information. ARZERRA (ofatumumab) Injection, for intravenous infusion. 2011. Available at: http://us.gsk.com/products/assets/us_arzerra.pdf. Accessed June 2012.

226. O'Brien S, Ravandi F, Riehl T, et al. Valganciclovir prevents cytomegalovirus reactivation in patients receiving alemtuzumab-based therapy. Blood 2008;111:1816-1819. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18039954.

227. Laurenti L, Piccioni P, Cattani P, et al. Cytomegalovirus reactivation during alemtuzumab therapy for chronic lymphocytic leukemia: incidence and treatment with oral ganciclovir. Haematologica 2004;89:1248-1252. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15477211.

228. Visani G, Mele A, Guiducci B, et al. An observational study of once weekly intravenous ganciclovir as CMV prophylaxis in heavily pre-treated chronic lymphocytic leukemia patients receiving subcutaneous alemtuzumab. Leuk Lymphoma 2006;47:2542-2546. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17169798.

229. O'Brien SM, Keating MJ, Mocarski ES. Updated guidelines on the management of cytomegalovirus reactivation in patients with chronic lymphocytic leukemia treated with alemtuzumab. Clin Lymphoma Myeloma 2006;7:125-130. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17026823.

230. Dearden C. Disease-specific complications of chronic lymphocytic leukemia. Hematology Am Soc Hematol Educ Program 2008;2008:450-456. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19074125.

231. Ding W, Zent CS. Diagnosis and management of autoimmune complications of chronic lymphocytic leukemia/ small lymphocytic

lymphoma. Clin Adv Hematol Oncol 2007;5:257-261. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17607284.

232. Borthakur G, O'Brien S, Wierda WG, et al. Immune anaemias in patients with chronic lymphocytic leukaemia treated with fludarabine, cyclophosphamide and rituximab – incidence and predictors. British Journal of Haematology 2007;136:800-805. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17341265.

233. Barcellini W, Capalbo S, Agostinelli R, et al. Relationship between autoimmune phenomena and disease stage and therapy in B-cell chronic lymphocytic leukemia. Haematologica 2006;91:1689-1692. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17145607.

234. Zanotti R, Frattini F, Ghia P, et al. ZAP-70 expression is associated with increased risk of autoimmune cytopenias in CLL patients. Am J Hematol 2010;85:494-498. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20575031.

235. Moreno C, Hodgson K, Ferrer G, et al. Autoimmune cytopenias in chronic lymphocytic leukemia: prevalence, clinical associations, and prognostic significance. Blood 2010;116:4771-4776. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20736453.

236. Visco C, Ruggeri M, Laura Evangelista M, et al. Impact of immune thrombocytopenia on the clinical course of chronic lymphocytic leukemia. Blood 2008;111:1110-1116. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17986663.

237. Cortes J, O'Brien S, Loscertales J, et al. Cyclosporin A for the treatment of cytopenia associated with chronic lymphocytic leukemia. Cancer 2001;92:2016-2022. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11596014.

238. D'Arena G, Laurenti L, Capalbo S, et al. Rituximab therapy for chronic lymphocytic leukemia-associated autoimmune hemolytic anemia. Am J Hematol 2006;81:598-602. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16823816.

239. Gupta N, Kavuru S, Patel D, et al. Rituximab-based chemotherapy for steroid-refractory autoimmune hemolytic anemia of chronic lymphocytic leukemia. Leukemia 2002;16:2092-2095. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12357362.

240. Berentsen S. Rituximab for the treatment of autoimmune cytopenias. Haematologica 2007;92:1589-1596. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18055980.

241. Godeau B, Porcher R, Fain O, et al. Rituximab efficacy and safety in adult splenectomy candidates with chronic immune thrombocytopenic purpura: results of a prospective multicenter phase 2 study. Blood 2008;112:925-926. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18463354.

242. Hegde UP, Wilson WH, White T, Cheson BD. Rituximab treatment of refractory fludarabine-associated immune thrombocytopenia in chronic lymphocytic leukemia. Blood 2002;100:2260-2262. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12200396.

243. Shanafelt TD, Madueme HL, Wolf RC, Tefferi A. Rituximab for immune cytopenia in adults: idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, and Evans syndrome. Mayo Clin Proc 2003;78:1340-1346. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14601692.

244. Ghazal H. Successful treatment of pure red cell aplasia with rituximab in patients with chronic lymphocytic leukemia. Blood 2002;99:1092-1094. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11807020.

245. Kuter DJ, Bussel JB, Lyons RM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. Lancet 2008;371:395-403. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18242413.

246. Kuter DJ, Rummel MJ, Boccia R, et al. Romiplostim or standard of care in patients with immune thrombocytopenia. New England Journal

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of Medicine 2010;363:1889-1899. Available at:
http://www.nejm.org/doi/abs/10.1056/NEJMoa1002625.

247. Bussel JB, Cheng G, Saleh MN, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. N Engl J Med 2007;357:2237-2247. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/18046028.

248. Bussel JB, Kuter DJ, Pullarkat V, et al. Safety and efficacy of long-term treatment with romiplostim in thrombocytopenic patients with chronic ITP. Blood 2009;113:2161-2171. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/18981291.

249. Dearden C, Wade R, Else M, et al. The prognostic significance of a positive direct antiglobulin test in chronic lymphocytic leukemia: a beneficial effect of the combination of fludarabine and cyclophosphamide on the incidence of hemolytic anemia. Blood 2008;111:1820-1826. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/18055869.

250. Celgene Corporation. Prescribing Information: REVLIMID [lenalidomide] capsules, for oral use. 2012 Available at:
http://www.revlimid.com/docs/Revlimid-Full-PI.pdf. Accessed November 2012

251. Bennett CL, Angelotta C, Yarnold PR, et al. Thalidomide- and lenalidomide-associated thromboembolism among patients with cancer. JAMA 2006;296:2558-2560. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/17148721.

252. Gay F, Hayman SR, Lacy MQ, et al. Lenalidomide plus dexamethasone versus thalidomide plus dexamethasone in newly diagnosed multiple myeloma: a comparative analysis of 411 patients. Blood 2010;115:1343-1350. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/20008302.

253. Palumbo A, Rajkumar SV, Dimopoulos MA, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma.

Leukemia 2008;22:414-423. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/18094721.

254. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol 2010;11:29-37. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/19853510.

255. Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med 2007;357:2133-2142. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/18032763.

256. Aue G, Nelson Lozier J, Tian X, et al. Inflammation, TNFalpha and endothelial dysfunction link lenalidomide to venous thrombosis in chronic lymphocytic leukemia. Am J Hematol 2011;86:835-840. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21812019.

AIDS-Related B-Cell Lymphoma

Overview

AIDS-related lymphoma is usually an AIDS-defining diagnosis in patients infected by the human immunodeficiency virus (HIV). Systemic lymphoma accounts for 70% to 90% of cases of HIV-associated lymphoma, while primary CNS lymphoma accounts for the remaining 10% to 30% of cases.[1-3] The distribution of systemic versus primary CNS lymphoma (PCNSL) may vary depending upon differences in factors such as geographic regions, time period covered and referral patterns of the institutions, between published reports. Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL) are the most common forms of systemic HIV-associated lymphoma.[2,3] In systemic cases of HIV-associated lymphomas, the BL histology is generally associated with a higher CD4+ cell count at diagnosis compared with DLBCL; cases of PCNSL is associated with much lower CD4+ count levels relative to systemic cases.[1,2]

Prior to the development of highly active antiretroviral therapy (HAART), HIV-associated lymphomas often presented with widespread, extra nodal disease, B symptoms, CNS involvement, and poor prognosis.[3] With the routine use of combination antiviral therapy in the HAART era, the prognosis of patients diagnosed with HIV-related NHL has improved, primarily for those with systemic lymphomas. In an early assessment of the shift in prognosis of patients with HIV-associated lymphomas between the pre-HAART (1993-1994) and HAART (1997-1998) eras, median overall survival (OS) improved from approximately 6 months in the pre-HAART years compared with 21 months in the HAART era for patients with systemic lymphomas; patients with PCNSL, however, continued to have poor prognosis, with a median OS less than 3 months during both periods.[2]

In a recent report from the COHERE (Collaboration of Observational HIV Epidemiological Research Europe) study evaluating outcomes of patients with HIV-associated lymphomas treated in the HAART era (1998-2006), the 1-year OS rates among patients with systemic lymphoma and PCNSL were 66% and 54%, respectively.[1] Although survival outcomes appear to be improving with contemporary therapies, outcomes for patients with PCNSL remain poor. Moreover, survival rates for patients with HIV-associated lymphomas remain low compared with patients with lymphomas unassociated with HIV infection; in a recent study, the 2-year OS rate for patients with HIV-associated lymphomas treated in the HAART era (1996-2005) was 41% compared with 70% in lymphoma patients without HIV infections.[4] Studies suggest that the improvement in prognosis observed with systemic HIV-associated lymphoma apply primarily to HIV-associated DLBCL but less to BL histology. In a study that investigated differences in outcomes by lymphoma histology and treatment era, median OS improved from 8 months (pre-HAART years: 1982-1996) to 38 months (HAART years: 1997-2003) among patients with HIV-associated DLBCL; contrastingly, OS outcomes remained poor (median 6 months to 5 months) during the same period among patients with HIV-associated BL.[5] BL histology appears to be associated with poorer survival outcomes among patients with HIV-associated lymphoma, even in the HAART era.[4,5]

Plasmablastic lymphoma (PBL) and primary effusion lymphoma (PEL) are two forms of lymphoma seen more commonly associated with HIV compared to lymphoma in patients without HIV infections. PEL accounts for less than 5% of HIV-associated lymphoma cases, most often occurring in the pleural, pericardial, and abdominal cavities.[6,7] PELs are associated with human herpes virus 8 (HHV8) infection and many are also co-infected with Epstein Barr virus (EBV). PBL is another unique large B-cell lymphoma that mainly involves the jaw and

oral cavity of HIV-infected patients.[8,9] Multicentric Castleman's disease (MCD) is prevalent in HIV-infected individuals, and has also been associated with HHV8 infection and increased incidence of lymphoma in HIV infected patients.[10]

Diagnosis

The diagnostic evaluation of HIV-associated lymphoma is not different from the non-HIV-associated disease. The major factor is to distinguish between BL and DLBCL. Hodgkin lymphoma and indolent lymphoma are seen in patients with HIV infection at an incidence higher than in the general population, but are much less common than BL or DLBCL.

Workup

The diagnostic evaluation and workup are as outlined in the NCCN Guidelines section for BL. However, all patients (without regard to histology) should have a lumbar puncture to rule out CNS involvement. In addition, baseline values for CD4 counts and HIV viral load should be obtained.

Treatment

Optimal management of HIV-associated lymphoma is not established. However, several key factors have emerged as being important to improve outcome. In general, studies have demonstrated that early introduction of HAART therapy is associated with superior outcomes. This has allowed for the administration of more dose-intense chemotherapy regimens and a reduction in treatment-associated toxicity.[11-13]

In prospective phase II studies, combination chemotherapy regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or CDE (cyclophosphamide, doxorubicin and etoposide)

given with concomitant HAART,[13-15] have proven to be active and tolerable in patients with HIV-associated lymphoma. The CHOP regimen has been shown to induce CR rates of 30% to 48%, with a median OS of approximately 25 months in patients with HIV-associated lymphomas.[14-16] The CDE regimen from the ECOG 1494 study demonstrated a CR rate of 45% with a 2-year OS of 43% in patients with HIV-associated lymphomas.[13] In a phase I/II study, combination therapy with CDOP (cyclophosphamide, liposomal doxorubicin, vincristine and prednisone) given with concomitant HAART showed high response rates (88% overall) in patients with HIV-associated lymphoma (N=24; DLBCL or variant in 79% of patients).[17] Liposomal doxorubicin was given at doses ranging from 40 to 80 mg/m^2, with fixed doses of the other three drugs. The CR rate with this regimen was 75%, and the median duration of CR was 16+ months; the OS rate at 1 year after start of therapy was 58%.[17] Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin) is another combination chemotherapy regimen that has been evaluated in patients with HIV-associated lymphoma. In a phase II study in previously untreated patients with HIV-associated NHL (N=39; 79% DLBCL; 18% BL), treatment with dose-adjusted EPOCH resulted in a ORR of 87% with a CR in 74% of patients.[18] At a median follow up of 53 months, progression-free survival (PFS) and OS rates were 73% and 60%, respectively. Only 2 of the patients with a CR experienced disease recurrence at last follow up (for a disease-free survival [DFS] rate of 92%). OS outcomes were decreased among the patients with low baseline CD4 counts (≤ 100/mcL) compared with those with higher CD4 counts (16% vs. 87%). Multivariate analysis using a Cox proportional hazard model showed that low CD4 counts and CNS involvement were the only significant factors associated with decreased OS.[18]

With the advent and wide availability of the anti-CD20 monoclonal antibody rituximab, the safety and efficacy of this immunotherapy agent in combination with chemotherapy has also been evaluated in clinical trials for patients with HIV-associated lymphomas. In the randomized phase III trial conducted by the AIDS Malignancies Consortium (AMC 010 study) in patients with HIV-associated NHL (N=150; 80% DLBCL; 9% BL), the addition of rituximab to CHOP (R-CHOP) was associated with improved CR rates (CR + unconfirmed CR [CRu]) compared with CHOP alone (58% vs. 47%); the median PFS was similar between treatment groups (10 months vs. 9 months) but both the median time to progression (29 months vs. 20 months) and OS (32 months vs. 25 months) were longer with R-CHOP.[16] These outcomes were not significantly different between treatment arms, however, and the R-CHOP combination was associated with increased risks of serious infections (including infection-related deaths in 14% of patients), particularly in patients with CD4+ counts of less than 50/mcL. It should also be noted that in this study, 35 patients randomized to the R-CHOP arm had received maintenance rituximab following initial R-CHOP.[16] In subsequent phase II trials, 6 cycles of the R-CHOP regimen showed CR/CRu rates of 69% to 77% in patients with HIV-associated NHL (majority with DLBCL histology), with manageable toxicities.[19,20] Infection-related deaths (regardless of attribution to study treatment) were reported in 2% to 9% of patients on these studies. In one study, the 2-year OS rate was 75%.[19] In the other study, the 3-year OS rate was 56% and the 3-year DFS rate among patients with a CR (measured from the time of documented CR) was 77%.[20] Rituximab in combination with infusional CDE (R-CDE) was also shown to be feasible and effective with an acceptable toxicity level in patients with HIV-associated lymphomas. In a phase II study in patients with primarily HIV-associated DLBCL histology (N=74; 72% DLBCL; 28% BL), the CR rate with R-CDE was 70% with

a 5-year OS rate of 56% and time-to-treatment-failure rate of 52%; among patients with a CR (measured from the time of documented CR), the 5-year DFS rate was 81%.[21,22] Infection-related deaths occurred in 8% of patients; 3% were considered related to study treatment. Rituximab was also evaluated in combination with infusional CDOP (R-CDOP) with concomitant antiretroviral therapy in a recent multicenter phase II trial (AMC 047 study) in patients with HIV-associated NHL (N=40; DLBCL in 98% of cases).[23] The ORR was 67.5% with a CR in 47.5%. The 1-year PFS and OS rates were 61% and 70%, respectively; the 2-year PFS and OS were 52% and 62%, respectively. Infectious complications were reported in 40% of patients (grade 4 in 5%) but no infection-related deaths occurred.[23] This may in part be explained by the fact that patients received concomitant HAART and those with low CD4 counts (≤ 100/mcL at baseline or during anti-tumor therapy) received antimicrobial prophylaxis. Factors such as decreased CD4 counts or increased HIV viral load did not appear to influence treatment response.[23] These results with the R-CDOP regimen, however, appeared less favorable compared with the EPOCH regimen discussed earlier (74% CR; 60% OS at median 53 months follow up)[18] or the EPOCH-R regimen (91% CR; 68% OS at median 5 years follow up),[24] discussed below.

The CODOX-M/IVAC regimen (cyclophosphamide, doxorubicin and high-dose methotrexate, alternating with ifosfamide, etoposide and high-dose cytarabine) with or without rituximab, is commonly used in the management of patients with BL. Retrospective studies suggest that this regimen may be applicable in patients with HIV-associated BL cases.[25,26] In a small retrospective analysis that included a subgroup of patients with HIV-associated BL treated with CODOX-M/IVAC (n=8), the CR rate was 63% with a 2-year event-free survival rate of 60%.[26] In a recent retrospective study of CODOX-M/IVAC with or without rituximab in patients with BL (N=80), similar outcomes were

observed between the subgroup of patients with HIV infection (n=14) and those without HIV infection (n=66).[25] The CR rates among patients with and without HIV infection were 93% and 88%, respectively; the 3-year PFS rate was 68% for both subgroups, and the 3-year OS rate was 68% and 72%, respectively. [25] This retrospective analysis also suggested that in the overall patient cohort, no significant differences in outcomes were observed with the addition of rituximab to CODOX-M/IVAC, although a trend toward improved 3-year PFS rate (74% vs. 61%) and OS rate (77% vs. 66%) with the addition of rituximab was noted. Among the small subgroup of patients with HIV-associated BL who received CODOX-M/IVAC with rituximab (n=10), 1 patient (10%) died due to a treatment-related infectious complication.[25]

The EPOCH regimen in combination with rituximab (EPOCH-R) has been shown to be effective and tolerable in patients with HIV-associated lymphomas.[24,27,28] In a study of dose-adjusted EPOCH with rituximab (DA-EPOCH-R) in patients with BL (N=23; including HIV-associated BL, n=8), the CR rate was 100% and both the PFS and OS rates at median 27 months of follow up was 100%.[27] More recently, the EPOCH-R regimen was evaluated using a short course of EPOCH with dose-dense rituximab in patients with HIV-associated DLBCL (N=33).[24] The CR rate with this regimen was 91%, and the PFS and OS rates were 84% and 68%, respectively, at a median follow up of 5 years.[24] In this study, the addition of rituximab did not appear to cause serious infection-related complications or deaths. The AMC 034 randomized trial evaluated the use of the EPOCH regimen in combination with sequential versus concurrent rituximab in patients with HIV-associated lymphomas (N=106; 75% DLBCL; 25% BL, BL-like).[28] The CR rate was 73% and 55% of patients in the concurrent (n=48 evaluable) and sequential (n=53 evaluable) arms, respectively; the 2-year PFS rate (66% vs. 63%) and OS rate (70% vs. 67%) were

similar between treatment arms.[28] Toxicity was comparable in the 2 treatment arms, although the concurrent regimen was associated with a higher incidence of treatment-related deaths among the patients with a baseline CD4+ count of less than 50/mcL. Overall, treatment-related deaths occurred in 5 patients (10%) in the concurrent arm (n=3 due to infections) and 4 patients (7%) in the sequential arm (n=3 due to infections). The authors concluded that concurrent EPOCH-R was an effective regimen for HIV-associated lymphoma, which merits further evaluation. The investigators from the aforementioned AMC trials (AMC 010 and AMC 034)[16,28] recently conducted a pooled analysis that included patients with HIV-associated NHL treated in the R-CHOP or EPOCH-R protocols (N=150 total).[29] The analysis was intended to evaluate patient/disease factors and treatment factors associated with outcomes. Factors such as low age-adjusted IPI score and baseline CD4 count 100/mcL or greater were significantly associated with improved CR rate, EFS and OS outcomes. Among the patients who were treated with concurrent EPOCH-R, both EFS and OS were significantly improved compared with R-CHOP (after adjusting for aaIPI and CD4 counts). The incidence of treatment-related deaths were higher in patients with low baseline CD4 counts (<50/mcL) compared with those with higher CD4 counts (37% vs. 6%; P<0.01).[29] The hyper-CVAD regimen (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine) with or without rituximab has also demonstrated high CR rates (64–92%) and a median OS of 12 months in patients with HIV-associated BL/leukemia and Burkitt-like lymphoma.[30,31]

The treatment of relapsed or refractory HIV-associated lymphomas remains a challenge, with autologous HSCT being the only potentially curative strategy, A recent retrospective analysis evaluated outcomes in patients with relapsed or refractory HIV-associated lymphoma

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treated with curative intent at AMC sites (13 sites, N=88).[32] The lymphoma diagnosis was NHL in the majority of patients (89%; the remainder had Hodgkin lymphoma [HL]). The most commonly used second-line regimens were ICE (ifosfamide, carboplatin and etoposide, 39%), dose adjusted EPOCH (19%) and ESHAP (etoposide, methylprednisone, cytarabine and cisplatin, 12.5%). Among the subgroup of patients with NHL, the ORR was 31% and the 1-year OS rate was 37%. Patients with a BL histology (n=12) appeared to have the worse outcomes with an ORR of 17% (compared with 33% in non-BL NHL) and a 1-year OS rate of only 12% (compared with 41.5% in non-BL NHL; P=0.005).[32] Among all patients (both NHL and HL), those with primary refractory disease (n=54) had significantly decreased ORR (24% vs. 56%; P=0.003) and decreased 1-year OS (31% vs. 59%; P=0.022) compared with those with relapsed disease. Baseline CD4 counts did not influence OS outcomes. Subsequent treatment with autologous HSCT was associated with improved 1-year OS (63% vs. 37%) compared with no transplant. However, for patients who experienced a response (CR or PR) after second-line therapy, no difference in 1-year OS was observed based on HSCT (87.5% with HSCT vs. 82% with no transplant).[32] For patients with relapsed/refractory HIV-associated NHL who can tolerate curative treatment regimens, autologous HSCT may offer the best chance for disease control. Although this retrospective analysis suggests that some patients may experience durable remission without HSCT, longer follow up data are needed.

PBL was associated with a poor prognosis in the pre-HAART era. In the HAART era, prognosis has improved with the use of intensive chemotherapy regimens along with HAART. The outcome of the HIV-positive patients with PBL treated at the Memorial Sloan-Kettering Cancer Center was reported to compare favorably to reports in the literature.[33] Among 6 patients treated with anthracycline-based multiagent chemotherapy in conjunction with HAART, 5 patients were alive and diseases free with a median follow-up of 22 months.[33] However, only limited data exist on the treatment approach for patients with PBL.

PCNSL is associated with severe immunosuppression and an overall poor prognosis. In retrospective analyses, patients with PCNSL treated with HAART and RT had a more favorable outcome.[34,35]

NCCN Recommendations

The NCCN Guidelines recommend the use of HAART and growth factor (e.g., G-CSF) support along with full-dose chemotherapy regimens. Any change in antiviral therapy should be made in consultation with an infectious disease specialist. Patients on antiretrovirals with persistently low CD4+ count of less than 50 to 100/mcL tend to have a poorer prognosis and higher risk of infection when being treated with rituximab-containing regimens.[16,21,28] Therefore, omission of rituximab is strongly suggested for these patients due to the higher risk of serious infectious complications. CNS prophylaxis with intrathecal methotrexate is used at some NCCN institutions for all patients, whereas at other NCCN institutions, only the patients with HIV-associated DLBCL with selected high-risk features (e.g., involvement of 2 or more extranodal sites with elevated LDH, bone marrow involvement, or other high-risk site involvement such as epidural, testicular or paranasal sinuses) receive upfront prophylaxis.

Recommended treatment regimens for patients with HIV-associated BL include dose-adjusted EPOCH with rituximab (DA-EPOCH-R), CODOX-M/IVAC (with or without rituximab), CDE with rituximab, or hyper-CVAD with rituximab. Recommended treatment options for patients with HIV-associated DLBCL include rituximab in combination

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with chemotherapy regimens such as dose-adjusted EPOCH, CDE or CHOP. The panel recommended DA-EPOCH-R as the preferred regimen for the treatment of HIV-associated BL and DLBCL. Patients with lymphoma associated with MCD and PEL can also be treated with the same regimens as described for patients with DLBCL. Since most cases of PEL are CD20-negative, the addition of rituximab to the chemotherapy regimen is not indicated.

The NCCN Guidelines recommend CODOX-M/IVAC, EPOCH or hyper-CVAD regimens for patients with PBL, with the realization that only limited data are available on the management of these patients at this time. High-dose methotrexate, RT or antiretroviral therapy can be considered for patients with PCNSL. Selected patients with good performance status receiving HAART may also be treated as per the NCCN Guidelines for Primary CNS Lymphoma.

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References

1. Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study group. Prognosis of HIV-associated non-hodgkin lymphoma in patients starting combination antiretroviral therapy. AIDS 2009;23:2029-2037. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19531926.

2. Besson C, Goubar A, Gabarre J, et al. Changes in AIDS-related lymphoma since the era of highly active antiretroviral therapy. Blood 2001;98:2339-2344. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11588028.

3. Levine AM, Seneviratne L, Espina BM, et al. Evolving characteristics of AIDS-related lymphoma. Blood 2000;96:4084-4090. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11110677.

4. Chao C, Xu L, Abrams D, et al. Survival of non-Hodgkin lymphoma patients with and without HIV infection in the era of combined antiretroviral therapy. AIDS 2010;24:1765-1770. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20453630.

5. Lim ST, Karim R, Nathwani BN, et al. AIDS-related Burkitt's lymphoma versus diffuse large-cell lymphoma in the pre-highly active antiretroviral therapy (HAART) and HAART eras: significant differences in survival with standard chemotherapy. J Clin Oncol 2005;23:4430-4438. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15883411.

6. Boulanger E, Gerard L, Gabarre J, et al. Prognostic factors and outcome of human herpesvirus 8-associated primary effusion lymphoma in patients with AIDS. J Clin Oncol 2005;23:4372-4380. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15994147.

7. Nador RG, Cesarman E, Chadburn A, et al. Primary effusion lymphoma: a distinct clinicopathologic entity associated with the Kaposi's sarcoma-associated herpes virus. Blood 1996;88:645-656. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8695812.

8. Delecluse HJ, Anagnostopoulos I, Dallenbach F, et al. Plasmablastic lymphomas of the oral cavity: a new entity associated with the human immunodeficiency virus infection. Blood 1997;89:1413-1420. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9028965.

9. Dong HY, Scadden DT, de Leval L, et al. Plasmablastic lymphoma in HIV-positive patients: an aggressive Epstein-Barr virus-associated extramedullary plasmacytic neoplasm. Am J Surg Pathol 2005;29:1633-1641. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16327436.

10. Mylona EE, Baraboutis IG, Lekakis LJ, et al. Multicentric Castleman's disease in HIV infection: a systematic review of the literature. AIDS Rev 2008;10:25-35. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18385778.

11. Cheung MC, Pantanowitz L, Dezube BJ. AIDS-related malignancies: emerging challenges in the era of highly active antiretroviral therapy. Oncologist 2005;10:412-426. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15967835.

12. Mounier N, Spina M, Gisselbrecht C. Modern management of non-Hodgkin lymphoma in HIV-infected patients. Br J Haematol 2007;136:685-698. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17229246.

13. Sparano JA, Lee S, Chen MG, et al. Phase II trial of infusional cyclophosphamide, doxorubicin, and etoposide in patients with HIV-associated non-Hodgkin's lymphoma: an Eastern Cooperative Oncology Group Trial (E1494). J Clin Oncol 2004;22:1491-1500. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15084622.

14. Ratner L, Lee J, Tang S, et al. Chemotherapy for human immunodeficiency virus-associated non-Hodgkin's lymphoma in combination with highly active antiretroviral therapy. J Clin Oncol 2001;19:2171-2178. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11304769.

15. Weiss R, Mitrou P, Arasteh K, et al. Acquired immunodeficiency syndrome-related lymphoma: simultaneous treatment with combined cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy and highly active antiretroviral therapy is safe and improves survival--results of the German Multicenter Trial. Cancer 2006;106:1560-1568. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16502436.

16. Kaplan LD, Lee JY, Ambinder RF, et al. Rituximab does not improve clinical outcome in a randomized phase 3 trial of CHOP with or without rituximab in patients with HIV-associated non-Hodgkin lymphoma: AIDS-Malignancies Consortium Trial 010. Blood 2005;106:1538-1543. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15914552.

17. Levine AM, Tulpule A, Espina B, et al. Liposome-encapsulated doxorubicin in combination with standard agents (cyclophosphamide, vincristine, prednisone) in patients with newly diagnosed AIDS-related non-Hodgkin's lymphoma: results of therapy and correlates of response. J Clin Oncol 2004;22:2662-2670. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15226333.

18. Little RF, Pittaluga S, Grant N, et al. Highly effective treatment of acquired immunodeficiency syndrome-related lymphoma with dose-adjusted EPOCH: impact of antiretroviral therapy suspension and tumor biology. Blood 2003;101:4653-4659. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12609827.

19. Boue F, Gabarre J, Gisselbrecht C, et al. Phase II trial of CHOP plus rituximab in patients with HIV-associated non-Hodgkin's lymphoma. J Clin Oncol 2006;24:4123-4128. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16896005.

20. Ribera JM, Oriol A, Morgades M, et al. Safety and efficacy of cyclophosphamide, adriamycin, vincristine, prednisone and rituximab in patients with human immunodeficiency virus-associated diffuse large B-cell lymphoma: results of a phase II trial. Br J Haematol 2008;140:411-419. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18162120.

21. Spina M, Jaeger U, Sparano JA, et al. Rituximab plus infusional cyclophosphamide, doxorubicin, and etoposide in HIV-associated non-Hodgkin lymphoma: pooled results from 3 phase 2 trials. Blood 2005;105:1891-1897. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15550484.

22. Spina M, Simonelli C, Vaccher E, et al. Long-term follow-up of rituximab and infusional cyclophosphamide, doxorubicin, and etoposide (CDE) in combination with HAART in HIV related Non-hodgkin's lymphomas (NHL)[abstract]. Blood 2008;112:Abstract 1467. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/112/11/1467.

23. Levine AM, Noy A, Lee JY, et al. Pegylated liposomal doxorubicin, rituximab, cyclophosphamide, vincristine, and prednisone in AIDS-related lymphoma: AIDS Malignancy Consortium Study 047. J Clin Oncol 2013;31:58-64. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23169503.

24. Dunleavy K, Little RF, Pittaluga S, et al. The role of tumor histogenesis, FDG-PET, and short-course EPOCH with dose-dense rituximab (SC-EPOCH-RR) in HIV-associated diffuse large B-cell lymphoma. Blood 2010;115:3017-3024. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20130244.

25. Barnes JA, Lacasce AS, Feng Y, et al. Evaluation of the addition of rituximab to CODOX-M/IVAC for Burkitt's lymphoma: a retrospective analysis. Ann Oncol 2011;22:1859-1864. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21339382.

26. Wang ES, Straus DJ, Teruya-Feldstein J, et al. Intensive chemotherapy with cyclophosphamide, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine (CODOX-M/IVAC) for human immunodeficiency virus-associated Burkitt lymphoma. Cancer 2003;98:1196-1205. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12973843.

27. Dunleavy K, Little RF, Pittaluga S. A prospective study of dose-adjusted (DA) EPOCH with rituximab in adult with newly diagnosed Burkitt lymphoma: A regimen with high efficacy and low toxicity. Annals of Oncology 2008;19 (suppl_4):iv83-84 Available at: http://annonc.oxfordjournals.org/content/19/suppl_4.

28. Sparano JA, Lee JY, Kaplan LD, et al. Rituximab plus concurrent infusional EPOCH chemotherapy is highly effective in HIV-associated B-cell non-Hodgkin lymphoma. Blood 2010;115:3008-3016. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20023215.

29. Barta SK, Lee JY, Kaplan LD, et al. Pooled analysis of AIDS malignancy consortium trials evaluating rituximab plus CHOP or infusional EPOCH chemotherapy in HIV-associated non-Hodgkin lymphoma. Cancer 2012;118:3977-3983. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22180164.

30. Cortes J, Thomas D, Rios A, et al. Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone and highly active antiretroviral therapy for patients with acquired immunodeficiency syndrome-related Burkitt lymphoma/leukemia. Cancer 2002;94:1492-1499. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11920506.

31. Thomas DA, Kantarjian HM, Cortes J, et al. Long-term outcome after hyper-CVAD and rituximab chemoimmunotherapy for Burkitt (BL) or Burkitt-like (BLL) leukemia/lymphoma and mature B-cell acute lymphocytic leukemia (ALL) [abstract]. Blood 2008;112:Abstract 1929. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/112/11/1929.

32. Bayraktar UD, Ramos JC, Petrich A, et al. Outcome of patients with relapsed/refractory acquired immune deficiency syndrome-related lymphoma diagnosed 1999-2008 and treated with curative intent in the AIDS Malignancy Consortium. Leuk Lymphoma 2012;53:2383-2389. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22642936.

33. Teruya-Feldstein J, Chiao E, Filippa DA, et al. CD20-negative large-cell lymphoma with plasmablastic features: a clinically heterogenous spectrum in both HIV-positive and -negative patients. Ann Oncol 2004;15:1673-1679. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15520070.

34. Newell ME, Hoy JF, Cooper SG, et al. Human immunodeficiency virus–related primary central nervous system lymphoma. Cancer 2004;100:2627-2636. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15197806.

35. Diamond C, Taylor TH, Im T, et al. Highly active antiretroviral therapy is associated with improved survival among patients with AIDS-related primary central nervous system non-Hodgkin's lymphoma. Curr HIV Res 2006;4:375-378. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16842088.

Cutaneous B-cell Lymphomas

Cutaneous B-cell lymphomas (CBCLs) are a group of B-cell lymphomas originating in and usually confined to the skin. CBCLs are estimated to represent approximately 20% to 25% of all primary cutaneous lymphomas.[1,2] In the United States, the SEER (Surveillance, Epidemiology, and End Results) data from the National Cancer Institute (NCI) indicated that the incidence of cutaneous T-cell lymphomas accounted for 71%, whereas CBCLs accounted for 29% from 2001 to 2005.[3] The WHO-EORTC classification for cutaneous lymphomas distinguishes 3 main types of CBCL[1,2]:

- Primary cutaneous marginal zone lymphoma (PC-MZL)
- Primary cutaneous follicle center cell lymphoma (PC-FCL)
- Primary cutaneous diffuse large B-cell, leg type (PC-DLBCL, leg type).

PC-FCL is the most common type of CBCL whereas PC-DLBCL leg type is less common. PC-MZL and PC-FCL are generally indolent or slow growing, whereas PC-DLBCL, leg type is usually an aggressive lymphoma associated with a generally poorer prognosis.[4-6] In an analysis of 300 patients with CBCL from the Dutch cutaneous lymphoma registry, PC-FCL, PC-MZL, and PC-DLBCL comprised 57%, 24%, and 19% of cases, respectively, based on the WHO-EORTC classification.[5] Extracutaneous relapse developed in 11%, 8.5%, and 46.5% of patients, respectively, demonstrating the higher incidence of extracutaneous progression associated with PC-DLBCL. The 5-year disease-specific OS rates in this series were 95%, 98%, and 50%, respectively. [5] In an Italian series of 467 patients with CBCL, PC-FCL and PC-MZL accounted for 57% and 31% of cases, respectively; PC-DLBCL leg type was reported in only 11% of patients.[6] While the various types of CBCL can occur anywhere on the skin, PC-FCL is

more prevalent in the scalp and the forehead, whereas the trunk and extremities are the most common sites for PC-MZL. Leg remains the most common, but not the only, site for PC-DLBCL. As noted previously, extracutaneous involvement is more frequent with PC-DLBCL, leg type.[5,6] In the same large Italian series, extracutaneous involvement eventually developed in 6% of patients with PC-MZL, 11% with PC-FCL, and 17% with PC-DLBCL, leg type.[6] In this study, radiotherapy was given as first-line treatment in 52.5% of patients and chemotherapy was given in 25% of patients. The 5-year overall survival (OS) rate was similar between patients with PC-MZL and PC-FCL (97% vs. 96%, respectively), but was significantly inferior in patients with PC-DLBCL, leg type, compared with either of the other 2 types of CBCL (73%; P<0.0001).[6] In patients with PC-MZL and PC-FCL, the disease-free survival (DFS) and OS rates were significantly higher for patients with single lesions compared with those with regional/disseminated lesions (5-year DFS, 62% vs. 44%; 5-year OS, 97% vs. 85%), whereas the difference in outcomes between single and regional/disseminated cutaneous involvement in patients with PC-DLBCL, leg type, was not significant (5-year DFS rate 55% vs. 44%; 5-year OS rate 79% vs. 67% for single and regional/disseminated lesions, respectively).[6]

Diagnosis

Adequate biopsy of the lesions and the slides should be reviewed by a pathologist with expertise in the diagnosis of primary CBCLs. Incisional, excisional or punch biopsy is preferred to shave biopsy, as CBCL have primarily dermal infiltrates, often deep, which are less well sampled and can even be missed by a shave biopsy. Adequate immunophenotyping with an immunohistochemistry (IHC) panel that evaluates B- and T-cell markers is needed to establish the diagnosis of the exact subtype of CBCL. The panel should include the following markers: CD20, CD79a, CD3, CD5, CD10, BCL2, BCL6, kappa/lambda and IRF4/MUM1. PC-

FCL is consistently BCL6-positive, whereas CD10 and BCL2 are expressed in only a few cases with a follicular growth pattern. PC-MZLs are always negative for BCL6 and CD10, but are often BCL2-positive.[7] Under certain circumstances, additional IHC studies may be useful to further establish the lymphoma subtype. These may include evaluation of additional markers such as Ki-67, CD43, CD21, and CD23, assessment of cyclin D1 using paraffin panels, and assessment of IgM and IgD expression.

While the diagnosis of PC-MZL is generally straightforward and reproducible among pathologists, it is more difficult to distinguish between PC-FCL and PC-DLBCL, leg type. Part of the difficulty is that cell size (i.e., large vs. small), is not a defining feature as it is in nodal B-cell lymphomas. Most patients with PC-FCL have lesions with a germinal center phenotype, whereas most with PC-DLBCL, leg type have an activated B-cell phenotype.[8] In nodal DLBCL, the germinal center phenotype is associated with a better prognosis than the activated B-cell phenotype. Both PC-FCL and PC-DLBCL are CD20 and BCL6 positive. BCL2 is usually negative in PC-FCL but highly expressed in PC-DLBCL, leg type. In addition, PC-FCL is usually MUM/IRF4-negative while PC-DLBCL, leg type is usually IRF4/MUM1-positive and show strong expression of FOXP1.[9] IRF4/MUM1 and FOXP1 may serve as additional diagnostic markers in the differential diagnosis of PC-FCL and PC-DLBCL. Additionally, assessment of surface IgM and IgD expression may also be helpful in distinguishing PC-DLBCL, leg type from PC-FCL.[10]

The t(14;18) translocation only rarely occurs in CBCLs. Therefore, the detection of a t(14;18) translocation in CBCL suggests the presence of systemic disease.[11] Molecular genetic analysis to detect *TCR* gene rearrangements and IgH gene rearrangements, and cytogenetics or FISH to detect t(14;18) may be useful in selected circumstances. If adequate biopsy material is available, flow cytometry analysis can be useful in determining B-cell clonality. The use of cyclin D1 may be useful to differentiate PC-MZL (negative for CD5 and cyclin D1) from mantle cell lymphomas (positive for CD5 and cyclin D1). Mantle cell lymphoma is not a primary cutaneous lymphoma and finding it in the skin requires a careful search for extracutaneous disease.

Workup

The initial workup is geared toward evaluating extent of disease on the skin and seeking extracutaneous disease. The absence of extracutaneous disease at diagnosis is part of the definition of primary CBCL. The workup includes a complete physical examination, a comprehensive skin examination and CT scans of the chest, abdomen and pelvis. PET-CT may have higher sensitivity in finding otherwise occult systemic disease, but this is not validated and the higher rates of false positive findings can create confusion. Bone marrow biopsy is essential for PC-DLBCL, leg type, whereas its role is unclear for PC-FCL and PC-MZL. Senff et al evaluated 275 patients with histological features consistent with marginal zone lymphoma (MZL; n=82) or follicle center lymphoma (FCL; n=193) first presenting in the skin.[12] Bone marrow involvement was seen in about 11% of patients in the FCL group compared with 2% in the MZL group. FCL patients with skin lesions and a positive bone marrow had a significantly worse prognosis compared with those with PC-FCL; the 5-year OS rate was 44% and 84%, respectively. [12]

The International Society of Cutaneous Lymphomas (ISCL) and the EORTC task force recommend that bone marrow biopsy be obtained for cutaneous lymphomas with intermediate to aggressive behaviors and should be considered for cutaneous lymphomas with indolent behavior and when there is any evidence of extracutaneous disease, as

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indicated by other staging assessments (e.g., radiographic evidence or serologic clues such as elevated monoclonal or polyclonal immunoglobulins).[13] The guidelines recommend considering bone marrow biopsy for patients with PC-FCL. It is optional for patients with PC-MZL. Peripheral blood flow cytometry will be useful in selected cases, if CBC demonstrates lymphocytosis.

Treatment

Primary CBCLs have a different clinical course and prognosis that distinguish them from their nodal counterparts. Treatment options for CBCLs depend on the histology and stage of the disease. Most commonly used therapies include excision, radiation therapy (RT), rituximab or systemic chemotherapy.[2,14]

In a large retrospective analysis by the Italian Study Group for Cutaneous Lymphomas involving 467 patients with CBCL, the complete remission (CR) rate, 5-and 10-year OS rates for all patients with PC-FCL and PC-MZL who received first-line treatment (RT in 52.5%, with total dose of 35–45 Gy; chemotherapy in 25%, mainly with CHOP; surgery in 23%) were 92% to 95%, 96% to 97% and 89% to 90.5%, respectively.[6] The relapse rate was 44% to 46.5% and extracutaneous spread was observed in 6% to 11% of patients. Relapse rate did not vary by type of initial therapy. In patients with PC-DLBCL, leg type, the CR rate, 5-and 10-year OS rates were 82%, 73% and 47%, respectively. PC-DLBCL, leg type was also associated with higher relapse rates (55%) and higher incidences of extracutaneous spread (17%). Among the patients with PC-DLBCL, a higher relapse rate was confirmed both for patients with single or regional lesions treated with RT and for patients with disseminated cutaneous involvement treated with chemotherapy.[6]

RT is very effective when used as initial local therapy as well as for cutaneous relapses in most patients with indolent CBCLs.[15-17] In patients with indolent histologies, RT and excision were associated with higher response rates compared to chemotherapy (98%, 97% and 76-86%, respectively) but were generally used for those with more limited disease so a direct comparison cannot be made.[6] The majority of patients with regional or disseminated disease will relapse regardless of type of initial treatment. However relapses are generally confined to the skin in which case survival does not appear to be affected.[6]

In a retrospective study of 34 patients with CBCL treated with RT, 5-year relapse-free survival (RFS) rates ranged from 62% to 73% for PC-FCL and PC-MZL but were only 33% for patients with PC-DLBCL, leg type.[17] The 5-year OS rate was 100% for PC-FCL and PC-MZL but was 67% for PC-DLBCL, leg type. Senff et al evaluated the outcome of 153 patients with CBCL (25 with PC-MZL; 101 with PC-FCL; and 27 with PC-DLBCL) that were initially treated with RT with a curative intent.[16] Overall, 45% of patients had single lesions while localized or disseminated lesions were seen in 43% and 12% of patients, respectively. CR was obtained in 151 of 153 patients (99%). Relapse rates for PC-MZL, PC-FCL, and PC-DLBCL, leg type were 60%, 29%, and 64%, and the 5-year disease-specific survival rate was 95%, 97%, and 59%, respectively. The PC-FCLs presenting on the legs also had a higher relapse rate (63%) and a lower 5-year disease-specific survival (44%) compared with PC-FCLs occurring at other sites (25% and 99%, respectively).[16]

Thus, local therapy is suitable for patients with indolent histologies, whereas patients with PC-DLBCL, leg type, which is associated with a more unfavorable clinical course, are generally treated with more aggressive treatment modalities—often with combined modality approaches as appropriate for systemic DLBCL.

NCCN Recommendations

Because there are no data from randomized clinical trials, the treatment recommendations included in the NCCN Guidelines are derived from the management practices of patients with CBCL at NCCN member institutions based on the limited data from retrospective analyses and studies involving small cohort of patients.

PC-FCL and PC-MZL

Initial Treatment

The NCCN Guidelines recommend local RT or excision as the initial treatment options for patients with solitary lesions or regional disease (T1-2). In select cases, patients may be considered for initial therapy with topical regimens (with steroids, imiquimod, or nitrogen mustard or bexarotene gel) or intralesional steroids.[2,18-23] Selected patients with local disease that is not amenable to local therapy (e.g., lesions on the scalp where hair loss is a major concern) can be observed.

For patients presenting with generalized skin lesions (T3), several treatment options are available. Chlorambucil has been shown to be effective in the treatment of PC-MZL with multifocal skin lesions.[24] In patients presenting with PC-FCL, multiagent chemotherapy or RT were equally effective for multifocal skin lesions.[18,25,26] Rituximab has shown activity as a treatment option for patients with indolent CBCLs with multiple lesions for which local therapy is not effective.[27-31] In a series of 16 patients with CBCL, 14 patients (87.5%) achieved a CR with rituximab monotherapy; 35% of these patients with CR eventually relapsed between 6 and 37 months.[31] In another retrospective analysis of 15 patients with indolent CBCLs, the overall response rate (ORR) was 87% (60% CR); the ORR was 100% for patients with PC-FCL and 60% for PC-MZL. With a median follow-up of 36 months, the median duration of response was 24 months.[30] Several case reports showed

the effectiveness of topical therapy using steroids, imiquimod, and nitrogen mustard or bexarotene gel.[18-22] Interlesional corticosteroids have also been used in the management of PC-FCL or PC-MZL, although only limited data are available.[2,23]

For patients presenting with generalized disease, the NCCN Guidelines have included observation, rituximab, topical therapy, local RT, intralesional steroids or systemic therapy (chlorambucil or cyclophosphamide, vincristine, prednisone [CVP]) with or without rituximab, as options. In patients with very extensive or symptomatic disease, other chemotherapy regimens recommended for the treatment of follicular lymphoma may be used. Patients presenting with extracutaneous disease should be managed according to the NCCN Guidelines section for follicular lymphoma.

Treatment for relapsed or refractory disease

While most of the patients respond to initial therapy, relapses do commonly occur. Patients with regional or localized relapse should receive additional therapy (excision, intralesional steroids, local RT or topical therapy using steroids, imiquimod, nitrogen mustard or bexarotene gel) and those with generalized disease relapse confined to the skin should receive additional therapy with treatment options recommended for generalized disease at presentation.

Patients with a PR or persistent progressive disease following additional treatment should be treated with the other options included in the listing of initial treatment to improve response before starting treatment for refractory disease. Patients with extracutaneous relapse or those with cutaneous relapse that are not responding to any of the initial treatment options should be managed according to the NCCN Guidelines section for follicular lymphoma.

PC-DLBCL, leg type

Initial Treatment

PC-DLBCL, leg type has a poorer prognosis than other types of CBCL, particularly in patients with multiple tumors on the legs. RT alone is less often effective in patients with PC-DLBCL. While these lesions do respond to RT, remissions are often short lived and higher rates of dissemination to extracutaneous sites occur. In a retrospective multicenter study from the French Study Group on 60 patients with PC-DLBCL, leg type, patients treated with anthracycline containing chemotherapy and rituximab had a more favorable short-term outcome, although no particular therapy (RT or multiagent chemotherapy with or without rituximab) was significantly associated with improved survival outcomes.[4] Among 12 patients treated with anthracycline-based chemotherapy with rituximab, the CR rate was 92% compared to 62% for patients who received other therapies. The 2-year OS rate for these two groups was 81% and 59%, respectively.[4] Recent case reports have also pointed to the potential utility of employing chemotherapy combined with rituximab in the management of patients with PC-DLBCL, leg type.[32,33]

For patients with localized disease, the NCCN Guidelines panel recommends local RT alone or in combination with R-CHOP. RT alone can be used in elderly patients or patients who are not able to tolerate systemic therapy. In patients with generalized disease, R-CHOP with or without RT is recommended. Extracutaneous disease should be managed according to the NCCN Guidelines section for DLBCL. The Guidelines recommend enrollment in clinical trials for all patients with PC-DLBCL, leg type, given the potentially aggressive nature of this disease.

Treatment for relapsed or refractory disease

In patients with regional relapses, R-CHOP is recommended if they have not received prior chemotherapy. Patients who have received prior chemotherapy should be treated with local RT or second-line chemotherapy regimens recommended for relapsed or refractory DLBCL. Local RT or second-line chemotherapy regimens recommended for relapsed or refractory DLBCL are the options for patients with generalized relapse. In a pilot study of 10 patients with relapsed CBCL, radioimmunotherapy (RIT) with yttrium-90 ibritumomab tiuxetan was shown to be effective with a CR rate of 100% and a median time to relapse of 12 months.[34] The NCCN Guidelines have included RIT as one of the treatment options for patients with relapsed PC-DLBCL.

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References

1. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005;105:3768-3785. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15692063.

2. Senff NJ, Noordijk EM, Kim YH, et al. European Organization for Research and Treatment of Cancer and International Society for Cutaneous Lymphoma Consensus recommendations for the management of cutaneous B-cell lymphomas. Blood 2008;112:1600-1609. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18567836.

3. Bradford PT, Devesa SS, Anderson WF, Toro JR. Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases. Blood 2009;113:5064-5073. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19279331.

4. Grange F, Beylot-Barry M, Courville P, et al. Primary cutaneous diffuse large B-cell lymphoma, leg type: clinicopathologic features and prognostic analysis in 60 cases. Arch Dermatol 2007;143:1144-1150. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17875875.

5. Senff NJ, Hoefnagel JJ, Jansen PM, et al. Reclassification of 300 primary cutaneous B-Cell lymphomas according to the new WHO-EORTC classification for cutaneous lymphomas: comparison with previous classifications and identification of prognostic markers. J Clin Oncol 2007;25:1581-1587. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17353548.

6. Zinzani PL, Quaglino P, Pimpinelli N, et al. Prognostic factors in primary cutaneous B-cell lymphoma: the Italian Study Group for Cutaneous Lymphomas. J Clin Oncol 2006;24:1376-1382. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16492713.

7. Hoefnagel JJ, Vermeer MH, Jansen PM, et al. Bcl-2, Bcl-6 and CD10 expression in cutaneous B-cell lymphoma: further support for a follicle centre cell origin and differential diagnostic significance. Br J Dermatol 2003;149:1183-1191. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14674895.

8. Hoefnagel JJ, Dijkman R, Basso K, et al. Distinct types of primary cutaneous large B-cell lymphoma identified by gene expression profiling. Blood 2005;105:3671-3678. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15308563.

9. Hoefnagel JJ, Mulder MMS, Dreef E, et al. Expression of B-cell transcription factors in primary cutaneous B-cell lymphoma. Mod Pathol 2006;19:1270-1276. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16778825.

10. Koens L, Vermeer MH, Willemze R, Jansen PM. IgM expression on paraffin sections distinguishes primary cutaneous large B-cell lymphoma, leg type from primary cutaneous follicle center lymphoma. Am J Surg Pathol 2010;34:1043-1048. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20551823.

11. Child F, Russell-Jones R, Woolford A, et al. Absence of the t(14;18) chromosomal translocation in primary cutaneous B-cell lymphoma. British Journal of Dermatology 2001;144:735-744. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11298531.

12. Senff N, Kluin-Nelemans H, Willemze R. Results of bone marrow examination in 275 patients with histological features that suggest an indolent type of cutaneous B-cell lymphoma. Br J Haematol 2008;142:52-56. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18422781.

13. Kim YH, Willemze R, Pimpinelli N, et al. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110:479-484. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17339420.

14. Willemze R. Primary cutaneous B-cell lymphoma: classification and treatment. Curr Opin Oncol 2006;18:425-431. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16894288.

15. Eich HT, Eich D, Micke O, et al. Long-term efficacy, curative potential, and prognostic factors of radiotherapy in primary cutaneous B-cell lymphoma. Int J Radiat Oncol Biol Phys 2003;55:899-906. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12605967.

16. Senff NJ, Hoefnagel JJ, Neelis KJ, et al. Results of radiotherapy in 153 primary cutaneous B-Cell lymphomas classified according to the WHO-EORTC classification. Arch Dermatol 2007;143:1520-1526. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18087001.

17. Smith BD, Glusac EJ, McNiff JM, et al. Primary cutaneous B-cell lymphoma treated with radiotherapy: a comparison of the European Organization for Research and Treatment of Cancer and the WHO classification systems. J Clin Oncol 2004;22:634-639. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14966086.

18. Bekkenk MW, Vermeer MH, Geerts ML, et al. Treatment of multifocal primary cutaneous B-cell lymphoma: a clinical follow-up study of 29 patients. J Clin Oncol 1999;17:2471-2478. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10561311.

19. Coors EA, Schuler G, Von Den Driesch P. Topical imiquimod as treatment for different kinds of cutaneous lymphoma. Eur J Dermatol 2006;16:391-393. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16935796.

20. Stavrakoglou A, Brown VL, Coutts I. Successful treatment of primary cutaneous follicle centre lymphoma with topical 5% imiquimod. Br J Dermatol 2007;157:620-622. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17553050.

21. Bachmeyer C, Orlandini V, Aractingi S. Topical mechlorethamine and clobetasol in multifocal primary cutaneous marginal zone-B cell lymphoma. British Journal of Dermatology 2006;154:1207-1209. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16704661.

22. Trent JT, Romanelli P, Kerdel FA. Topical targretin and intralesional interferon alfa for cutaneous lymphoma of the scalp. Arch Dermatol

2002;138:1421-1423. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12437444.

23. Perry A, Vincent BJ, Parker SR. Intralesional corticosteroid therapy for primary cutaneous B-cell lymphoma. Br J Dermatol 2010;163:223-225. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20394622.

24. Hoefnagel JJ, Vermeer MH, Jansen PM, et al. Primary cutaneous marginal zone B-cell lymphoma: clinical and therapeutic features in 50 cases. Arch Dermatol 2005;141:1139-1145. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16172311.

25. Rijlaarsdam JU, Toonstra J, Meijer OW, et al. Treatment of primary cutaneous B-cell lymphomas of follicle center cell origin: a clinical follow-up study of 55 patients treated with radiotherapy or polychemotherapy. J Clin Oncol 1996;14:549-555. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8636770.

26. Brice P, Cazals D, Mounier N, et al. Primary cutaneous large-cell lymphoma: analysis of 49 patients included in the LNH87 prospective trial of polychemotherapy for high-grade lymphomas. Groupe d'Etude des Lymphomes de l'Adulte. Leukemia 1998;12:213-219. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9519784

27. Gellrich S, Muche JM, Wilks A, et al. Systemic eight-cycle anti-CD20 monoclonal antibody (rituximab) therapy in primary cutaneous B-cell lymphomas--an applicational observation. Br J Dermatol 2005;153:167-173. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16029344.

28. Heinzerling LM, Urbanek M, Funk JO, et al. Reduction of tumor burden and stabilization of disease by systemic therapy with anti-CD20 antibody (rituximab) in patients with primary cutaneous B-cell lymphoma. Cancer 2000;89:1835-1844. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11042581.

29. Heinzerling L, Dummer R, Kempf W, et al. Intralesional therapy with anti-CD20 monoclonal antibody rituximab in primary cutaneous B-cell

lymphoma. Arch Dermatol 2000;136:374-378. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/10724200.

30. Morales AV, Advani R, Horwitz SM, et al. Indolent primary
cutaneous B-cell lymphoma: experience using systemic rituximab. J Am
Acad Dermatol 2008;59:953-957. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/18817999.

31. Valencak J, Weihsengruber F, Rappersberger K, et al. Rituximab
monotherapy for primary cutaneous B-cell lymphoma: response and
follow-up in 16 patients. Ann Oncol 2009;20:326-330. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/18836086.

32. Posada Garcia C, Florez A, Pardavila R, et al. Primary cutaneous
large B-cell lymphoma, leg type, successfully treated with rituximab plus
chemotherapy. Eur J Dermatol 2009;19:394-395. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/19467966.

33. Grange F, Maubec E, Bagot M, et al. Treatment of cutaneous B-cell
lymphoma, leg type, with age-adapted combinations of chemotherapies
and rituximab. Arch Dermatol 2009;145:329-330. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/19289772.

34. Maza S, Gellrich S, Assaf C, et al. Yttrium-90 ibritumomab tiuxetan
radioimmunotherapy in primary cutaneous B-cell lymphomas: first
results of a prospective, monocentre study. Leuk Lymphoma
2008;49:1702-1709. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/18661405.

Hairy Cell Leukemia

Diagnosis

Hairy cell leukemia (HCL) is a rare type of indolent B-cell leukemia comprising about 2% of all lymphoid leukemias.[1] Leukemic cells typically infiltrate the bone marrow and spleen, and may also be found in the liver and lymph nodes. Clinically, HCL is characterized by symptoms of fatigue and weakness, and most patients will present with splenomegaly (symptomatic or asymptomatic) and pancytopenia.[1,2] In addition, patients may present with hepatomegaly and/or lymphadenopathy. Patients may also present with recurrent opportunistic infections.[1,2]

Morphological evaluation of peripheral blood smears and bone marrow biopsy, as well as adequate immunophenotyping by immunohistochemistry (IHC) and/or flow cytometry are essential to establish the diagnosis of HCL. Leukemic cells in HCL are small to medium in size, showing a round, oval or indented nucleus with a well-defined nuclear border. The presence of a cytoplasm with prominent hair-like projections is characteristic of HCL.[3,4] Examination of bone marrow biopsy samples shows hairy cell infiltrates with increased reticulin fibers, which frequently results in a "dry" tap. In some patients with HCL, the bone marrow may show hypocellularity; this is important to recognize in order to avoid an erroneous diagnosis of aplastic anemia.[3,4] As mentioned above, immunophenotyping is essential in establishing the diagnosis. It is also necessary in distinguishing the variant form of HCL from classic HCL, as HCL variant tends to be associated with a more aggressive disease course and may not respond to standard HCL therapies.[4,5] In the 2008 WHO classification, HCL variant is considered a separate entity that is biologically distinct from classic HCL.[4] The IHC panel for immunophenotyping should include the following markers: CD20, CD25, CD123, and cyclin D1.

Annexin A1 may be useful under certain circumstances. In addition, the following markers should be included for analysis by flow cytometry: CD3, CD5, CD10, CD11c, CD19, CD20, CD22, CD25, and CD103. The typical immunophenotype for classic HCL shows CD5-, CD10- CD11c+(bright), CD20+(bright), CD22+(bright), CD25+(bright), CD103+, CD123+ (bright), cyclin D1+, and Annexin A1+.[1,2,6,7] In contrast, HCL variant is uniformly CD25- and Annexin A1-.[1,2,6]

Consistent with the postulation that HCL originates from post-germinal center B-cells, the large majority of HCL cases (80–90%) show immunoglobulin heavy chain variable (*IGHV*) genes with somatic hypermutation.[1,8,9] Unmutated *IGHV* status in HCL has been associated with primary refractoriness to single-agent therapy with a purine nucleoside analog, and more rapid disease progression.[9] Thus, unmutated *IGHV* may serve as a prognostic factor for poorer outcomes with conventional therapies. The V600E mutation of the *BRAF* gene was recently identified in patients with HCL.[10] During the last year, several published reports have consistently demonstrated the presence of *BRAF* V600E mutation in all tested cases of HCL, while the mutation was absent in other cases of B-cell leukemias or lymphomas.[10-13] Interestingly, recent studies reported the absence of *BRAF* V600E mutation in HCL variant cases,[6,14] and in a small group of classic HCL cases; in the latter, about half of the *BRAF* wildtype cases also showed *VH4-34* rearrangement of the *IGHV* gene.[14] Although further studies are needed, the *BRAF* V600E mutation may potentially serve as a reliable molecular marker that distinguishes HCL from other B-cell lymphoproliferative disorders. Moreover, the presence of this mutation may have implications for the use of new targeted therapies for HCL. Under certain circumstances, molecular analysis to determine *IGHV* gene mutational status and to detect *BRAF* V600E mutation may be useful.

Workup

The initial workup for newly diagnosed HCL should include a thorough physical examination with attention to palpable enlargement of the spleen, liver, and/or lymph nodes (although presence of peripheral lymphadenopathy is uncommon), and evaluation of performance status. Laboratory assessments should include standard blood work including CBC with differential and a comprehensive metabolic panel. In particular, close evaluation of renal function is advised considering the renal route of excretion of drugs (e.g., pentostatin) used in the treatment of HCL. In addition, measurements of serum lactate dehydrogenase (LDH) levels should be obtained. A bone marrow biopsy, with or without aspirates, should be obtained. Hepatitis B virus (HBV) testing is recommended due to increased risks of viral reactivation when immunotherapy regimens containing rituximab are being considered for treatment. Under certain circumstances, CT scans (with contrast of diagnostic quality) of the chest, abdomen and/or pelvis may be useful.

Treatment Options

During the last several decades, the treatment strategy for patients with HCL has evolved from the use of interferon to single-agent purine analogs to the incorporation of targeted immunotherapy with rituximab. Interferon alpha was the first therapeutic agent to show activity in the treatment of HCL (as both induction and maintenance therapy) and long-term results from this agent suggested that durable disease control can be achieved.[15-17] With the introduction of purine analogs such as pentostatin and cladribine, the initial treatment for HCL largely shifted to the use of these agents. As a single agent, pentostatin has been shown to induce a response in nearly all patients with HCL, with high complete response (CR) rates of 75-90%.[18-24] This is in contrast to the lower CR rates (about 15%) reported with interferon alpha.[16,17,21]

In the randomized phase III intergroup study that evaluated pentostatin versus interferon alpha in patients with previously untreated HCL (N=313 evaluable), pentostatin resulted in significantly higher CR rates (76% vs. 11%; P<0.0001) and longer median relapse-free survival (not reached vs. 20 months; P<0.0001; after a median follow up of 57 months) compared with interferon alpha.[21] Survival outcomes were not significantly different between treatment arms, although this analysis was complicated by the cross-over design of the study. Results from long-term follow up of studies with pentostatin reported 10-year disease-free survival (DFS) rates of about 65% to 70%, and 10-year overall survival (OS) rates of 80% to 90%; the median DFS was about 16 years.[18,20,23] These favorable outcomes were observed even in studies in which the majority of patients were previously treated,[23] or cross-over to pentostatin was permitted after failure with initial interferon treatment.[20,21] The most common toxicities reported in the randomized phase III study with pentostatin were grade 3-4 neutropenia (20%) and infections (any grade; 53%) including those requiring intravenous antibiotics (27%).[21] In the retrospective study in a large number of patients treated with pentostatin (N=238), the most common toxicities were grade 3-4 thrombocytopenia (15%), grade 3-4 neutropenia (8%), febrile neutropenia (17%), and documented infections (6%); it should be noted that in this analysis, data from patients with pre-existing cytopenias were excluded for the first 2 months of treatment.[23]

Cladribine is another purine analog with significant activity in HCL. As a single agent, cladribine has also been reported to induce high CR rates of 80% to 98%.[18,19,25-31] Long-term follow up data showed a median DFS or remission duration of over 8 years, and a 12-year OS rate of about 80% to 90%.[25-27,31] Different routes of administration (subcutaneous bolus versus intravenous continuous infusion) and dosing schedules (e.g., daily versus weekly) of cladribine have been

evaluated, which showed similar activity and toxicity profiles.[32-35] The most common toxicities with cladribine were grade 3-4 neutropenia (occurring in the large majority of patients; about 65–85%), febrile neutropenia (about 40%), grade 3-4 thrombocytopenia (about 20%) and infections (about 10%).[29-31]

Overall, outcomes with single-agent pentostatin or cladribine appear comparable, with both agents demonstrating durable remissions in patients with HCL.[18,36] Moreover, both agents have been shown to induce second or subsequent CRs in a large proportion of patients who received retreatment with the same agent at relapse following initial therapy; these subsequent responses were generally durable, albeit shorter with successive treatments.[18,26,29] Results from long-term follow up with purine analogs reported that about 35% to 40% of patients eventually relapse after first-line treatment.[18,25,26,36] In the long-term follow up data from the Scripps Research Institute in patients treated with cladribine (N=207 evaluable with long-term data), the CR rate with initial therapy was 95%; the median response duration for all responders was 98 months (range, 8–172 months).[26] Relapse occurred in 37% of initial responders, with a median time to relapse of 42 months (range, 8–118 months). Among the patients with relapsed disease who received retreatment with cladribine (n=59), the CR rate was 75%; the median duration of second response was 35 months.[26] Subsequently, 20 of these responders (33%) experienced a second relapse and 10 patients were retreated again with cladribine. The CR rate was 60% in these patients, with median response duration of 20 months.[26] Thus, for patients who relapse after an initial durable remission to purine analog therapy, retreatment with the same agent may yield a reasonable duration of disease control. Treatment with an alternative purine analog has been shown to induce similar rates of second remissions in patients who experience relapse.[23,36]

Given the observation that retreatment with purine analogs resulted in shorter remission durations with each successive treatment, other agents have been investigated in the management of patients with HCL relapsing after purine analog therapies. One such agent is rituximab, a chimeric anti-CD20 monoclonal antibody with substantial activity in B-cell lymphomas and leukemias. CD20 is typically highly expressed in HCL cases, and therefore represents a potential target for therapy. Several studies have evaluated the role of single-agent rituximab in patients with HCL that relapsed after purine analog treatments. [37-40] In an early study in a small number of patients (N=10), rituximab given at standard doses (375 mg/m^2 weekly for 4 weeks) resulted in an ORR of 50% with CR in only 10% of patients.[37] Patients had received a median of 2 prior treatments (range, 2–3) prior to rituximab. In a phase II study in patients with relapsed HCL after cladribine (N=24), rituximab induced an ORR of only 25% with CR in 13%.[38] These patients had also received a median of 2 prior therapies (range, 1–4), although none were considered refractory to their prior treatments. In another phase II study in less heavily pretreated patients with HCL relapsing after cladribine (N=25; median 1 prior therapy), the ORR and CR rate with rituximab was 80% and 32%, respectively.[40] In a smaller study that used 8 weekly doses of rituximab (rather than the standard 4 weekly doses) in patients with relapsed HCL (N=15; more than 1 prior therapy in 53%), the ORR and CR rate was 80% and 53%, respectively.[39] Among responding patients, 5 (42%) experienced disease relapse at a median 18 months from start of treatment.

As shown from the studies mentioned above, rituximab given as single-agent therapy appears to have modest activity, at best, in patients with relapsed HCL. Recent studies have evaluated rituximab in combination (concurrent or sequential) with purine analogs in both relapsed/refractory and previously untreated HCL.[41-44] In a

retrospective study in patients with pretreated HCL relapsing after single-agent purine analog treatments (N=18; median 2 prior therapies, range 1–6), rituximab combined with pentostatin or cladribine resulted in a CR rate of 89%.[41] CR was maintained in all patients after a median follow up of 36 months. The estimated 3-year recurrence rate was 7% with this combination approach.[41] In a recent phase II study, cladribine followed (sequentially) by rituximab (8 weekly doses) was evaluated in previously untreated patients with HCL (N=36; including HCL variant, n=5).[44] All patients achieved a CR with this regimen. After a median follow up of 25 months, the duration of CR has not yet been reached. Disease relapse occurred in 1 patient with HCL variant.[44] Among the patients with classic HCL who were assessed for minimal residual disease (MRD) at the end of treatment, MRD negativity was demonstrated in 79% of patients based on multiparameter flow cytometry and in 70% by consensus primer PCR assay.[44] Grade 3-4 infections occurred in 33% of patients (resolved in all). The regimen was otherwise well tolerated, with no other grade 3-4 non-hematologic toxicities reported.[44] In a small retrospective analysis of data from patients with relapsed/refractory HCL treated with a different purine analog (fludarabine) combined with rituximab (N=15), response was achieved in all patients (although categorization of CR versus PR was not available).[45] Fourteen patients (93%) remained progression free at a median follow up of 35 months; 1 patient died from progressive disease. The 5-year progression-free survival rate and OS rate was 89% and 83%, respectively.[45] Further prospective studies are needed to confirm these promising outcomes with fludarabine combined with rituximab.

Investigational agents for the treatment of HCL include recombinant immunotoxin (e.g., BL22 and HA22, a protein comprising anti-CD22 antibody fragment fused to a bacterial exotoxin), which has shown promising response rates (about 70–85% ORR; 45% CR) in phase I/II

studies.[46,47] As briefly mentioned above, targeting of the *BRAF* mutation may also hold promise for future investigation in HCL therapy. Vemurafenib is an orally administered inhibitor of mutated forms of the BRAF kinase, including V600E-mutated BRAF kinase, and is currently approved for the treatment of patients with metastatic or unresectable melanoma harboring the *BRAF* V600E mutation.[48] In 2 recent case reports, treatment with vemurafenib resulted in a CR in patients with HCL who were refractory to or relapsed after conventional therapies (including with purine analogs).[49,50] Although promising, the use of this agent is investigational in patients with HCL, and data from large clinical trials are needed to evaluate the role of BRAF inhibitors in HCL. An ongoing phase II study is evaluating the efficacy and safety of vemurafenib in patients with relapsed and/or refractory HCL (NCT01711632 registered at clinicaltrials.gov).

NCCN Recommendations

Clinical judgement is required in the decision to initiate therapy, as not all newly diagnosed patients with HCL will require immediate treatment. Indications for treatment initiation may include symptomatic disease with debilitating fatigue, physical discomfort due to splenomegaly, and/or cytopenias. Patients who are asymptomatic may be best managed by close observation ("watch and wait" approach) until indications develop.

The current NCCN Guidelines apply to cases of classic HCL, and not the HCL variant; at the present time, sufficient data are not available to determine the optimal management of HCL variant cases.

Initial Therapy and Follow Up
For patients with indications for treatment, the NCCN Guidelines panel recommends first-line therapy with either of the purine analogs cladribine or pentostatin. Data from randomized controlled trials are

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not available to compare the efficacy of one purine analog to the other, and both agents have been extensively evaluated in clinical studies in HCL. In general, cladribine should be avoided in patients with an active life-threatening infection or recurrent (chronic) infections.

Patients who achieve a CR with initial purine analog therapy should be observed until indications for additional treatment (disease relapse). CR is defined as normalization of blood counts (e.g., hemoglobin >12 g/dL, absolute neutrophil count >1,500/mcL, platelets >100,000/mcL) absence of HCL cells by morphological examination of bone marrow biopsy or peripheral blood samples, resolution of organomegaly by physical examination, and absence of disease symptoms.[3] The role of MRD status in responding patients remain uncertain at this time. Patients with less than a CR to initial therapy should be managed similarly to patients who relapse within 1 year after a CR (see "Second-line therapy" below).

Second-line Therapy

Treatment options for patients with relapsed/refractory HCL depend upon the quality and duration of remission to initial therapy.[3] As mentioned in the discussion above, patients who achieve a durable CR to initial therapy may benefit from retreatment with the same agent. For patients with a durable CR (i.e., those who relapse after 1 year or later from initial response), second-line treatment options include retreatment with the same purine analog with or without rituximab, or treatment with an alternative purine analog with or without rituximab. For patients with a CR who relapse within 1 year of initial response, or for patients with less than a CR to initial therapy, second-line treatment options include participation in a clinical trial (if available), an alternative purine analog with or without rituximab, rituximab alone or interferon alpha.

References

1. Foucar K, Falini B, Catovsky D, Stein H. Hairy cell leukaemia. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO Classification of Tumours or Haematopoietic and Lymphoid Tissues (ed 4th). Lyon: IARC; 2008.

2. Grever MR, Lozanski G. Modern strategies for hairy cell leukemia. J Clin Oncol 2011;29:583-590. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21220590.

3. Grever MR. How I treat hairy cell leukemia. Blood 2010;115:21-28. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19843881.

4. Piris M, Foucar K, Mollejo M, et al. Splenic B-cell lymphoma/leukaemia, unclassifiable. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO Classification of Tumours or Haematopoietic and Lymphoid Tissues (ed 4th). Lyon: IARC; 2008.

5. Robak T. Hairy-cell leukemia variant: recent view on diagnosis, biology and treatment. Cancer Treat Rev 2011;37:3-10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20558005.

6. Shao H, Calvo KR, Gronborg M, et al. Distinguishing hairy cell leukemia variant from hairy cell leukemia: development and validation of diagnostic criteria. Leuk Res 2013;37:401-409. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23347903.

7. Stetler-Stevenson M, Tembhare PR. Diagnosis of hairy cell leukemia by flow cytometry. Leuk Lymphoma 2011;52 Suppl 2:11-13. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21504292.

8. Arons E, Sunshine J, Suntum T, Kreitman RJ. Somatic hypermutation and VH gene usage in hairy cell leukaemia. Br J Haematol 2006;133:504-512. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16681637.

9. Forconi F, Sozzi E, Cencini E, et al. Hairy cell leukemias with unmutated IGHV genes define the minor subset refractory to single-agent cladribine and with more aggressive behavior. Blood 2009;114:4696-4702. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19667403.

10. Tiacci E, Trifonov V, Schiavoni G, et al. BRAF mutations in hairy-cell leukemia. N Engl J Med 2011;364:2305-2315. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21663470.

11. Andrulis M, Penzel R, Weichert W, et al. Application of a BRAF V600E mutation-specific antibody for the diagnosis of hairy cell leukemia. Am J Surg Pathol 2012;36:1796-1800. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22531170.

12. Arcaini L, Zibellini S, Boveri E, et al. The BRAF V600E mutation in hairy cell leukemia and other mature B-cell neoplasms. Blood 2012;119:188-191. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22072557.

13. Boyd EM, Bench AJ, van 't Veer MB, et al. High resolution melting analysis for detection of BRAF exon 15 mutations in hairy cell leukaemia and other lymphoid malignancies. Br J Haematol 2011;155:609-612. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21910720.

14. Xi L, Arons E, Navarro W, et al. Both variant and IGHV4-34-expressing hairy cell leukemia lack the BRAF V600E mutation. Blood 2011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22210875.

15. Benz R, Siciliano RD, Stussi G, Fehr J. Long-term follow-up of interferon-alpha induction and low-dose maintenance therapy in hairy cell leukemia. Eur J Haematol 2009;82:194-200. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19077050.

16. Damasio EE, Clavio M, Masoudi B, et al. Alpha-interferon as induction and maintenance therapy in hairy cell leukemia: a long-term follow-up analysis. Eur J Haematol 2000;64:47-52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10680705.

17. Federico M, Frassoldati A, Lamparelli T, et al. Long-term results of alpha interferon as initial therapy and splenectomy as consolidation therapy in patients with hairy cell leukemia. Final report from the Italian Cooperative Group for HCL. Ann Oncol 1994;5:725-731. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7826905.

18. Dearden CE, Else M, Catovsky D. Long-term results for pentostatin and cladribine treatment of hairy cell leukemia. Leuk Lymphoma 2011;52 Suppl 2:21-24. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21599603.

19. Else M, Dearden CE, Matutes E, et al. Long-term follow-up of 233 patients with hairy cell leukaemia, treated initially with pentostatin or cladribine, at a median of 16 years from diagnosis. Br J Haematol 2009;145:733-740. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19344416.

20. Flinn IW, Kopecky KJ, Foucar MK, et al. Long-term follow-up of remission duration, mortality, and second malignancies in hairy cell leukemia patients treated with pentostatin. Blood 2000;96:2981-2986. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11049974.

21. Grever M, Kopecky K, Foucar MK, et al. Randomized comparison of pentostatin versus interferon alfa-2a in previously untreated patients with hairy cell leukemia: an intergroup study. J Clin Oncol 1995;13:974-982. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7707126.

22. Kraut EH, Bouroncle BA, Grever MR. Low-dose deoxycoformycin in the treatment of hairy cell leukemia. Blood 1986;68:1119-1122. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3490287.

23. Maloisel F, Benboubker L, Gardembas M, et al. Long-term outcome with pentostatin treatment in hairy cell leukemia patients. A French retrospective study of 238 patients. Leukemia 2003;17:45-51. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12529659.

24. Spiers AS, Parekh SJ, Bishop MB. Hairy-cell leukemia: induction of complete remission with pentostatin (2'-deoxycoformycin). J Clin Oncol 1984;2:1336-1342. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6334721.

25. Chadha P, Rademaker AW, Mendiratta P, et al. Treatment of hairy cell leukemia with 2-chlorodeoxyadenosine (2-CdA): long-term follow-up of the Northwestern University experience. Blood 2005;106:241-246. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15761021.

26. Goodman GR, Burian C, Koziol JA, Saven A. Extended follow-up of patients with hairy cell leukemia after treatment with cladribine. J Clin Oncol 2003;21:891-896. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12610190.

27. Jehn U, Bartl R, Dietzfelbinger H, et al. An update: 12-year follow-up of patients with hairy cell leukemia following treatment with 2-chlorodeoxyadenosine. Leukemia 2004;18:1476-1481. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15229616.

28. Piro LD, Carrera CJ, Carson DA, Beutler E. Lasting remissions in hairy-cell leukemia induced by a single infusion of 2-chlorodeoxyadenosine. N Engl J Med 1990;322:1117-1121. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1969613.

29. Saven A, Burian C, Koziol JA, Piro LD. Long-term follow-up of patients with hairy cell leukemia after cladribine treatment. Blood 1998;92:1918-1926. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9731048.

30. Tallman MS, Hakimian D, Variakojis D, et al. A single cycle of 2-chlorodeoxyadenosine results in complete remission in the majority of patients with hairy cell leukemia. Blood 1992;80:2203-2209. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1358262.

31. Zinzani PL, Tani M, Marchi E, et al. Long-term follow-up of front-line treatment of hairy cell leukemia with 2-chlorodeoxyadenosine. Haematologica 2004;89:309-313. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15020269.

32. Lauria F, Bocchia M, Marotta G, et al. Weekly administration of 2-chlorodeoxyadenosine in patients with hairy-cell leukemia is effective and reduces infectious complications. Haematologica 1999;84:22-25. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10091389.

33. Robak T, Jamroziak K, Gora-Tybor J, et al. Cladribine in a weekly versus daily schedule for untreated active hairy cell leukemia: final report from the Polish Adult Leukemia Group (PALG) of a prospective, randomized, multicenter trial. Blood 2007;109:3672-3675. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17209059.

34. von Rohr A, Schmitz SF, Tichelli A, et al. Treatment of hairy cell leukemia with cladribine (2-chlorodeoxyadenosine) by subcutaneous bolus injection: a phase II study. Ann Oncol 2002;13:1641-1649. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12377655.

35. Zenhausern R, Schmitz SF, Solenthaler M, et al. Randomized trial of daily versus weekly administration of 2-chlorodeoxyadenosine in patients with hairy cell leukemia: a multicenter phase III trial (SAKK 32/98). Leuk Lymphoma 2009;50:1501-1511. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19672771.

36. Else M, Ruchlemer R, Osuji N, et al. Long remissions in hairy cell leukemia with purine analogs: a report of 219 patients with a median follow-up of 12.5 years. Cancer 2005;104:2442-2448. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16245328.

37. Lauria F, Lenoci M, Annino L, et al. Efficacy of anti-CD20 monoclonal antibodies (Mabthera) in patients with progressed hairy cell leukemia. Haematologica 2001;86:1046-1050. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11602410.

38. Nieva J, Bethel K, Saven A. Phase 2 study of rituximab in the treatment of cladribine-failed patients with hairy cell leukemia. Blood 2003;102:810-813. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12663446.

39. Thomas DA, O'Brien S, Bueso-Ramos C, et al. Rituximab in relapsed or refractory hairy cell leukemia. Blood 2003;102:3906-3911. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12816862.

40. Zenhausern R, Simcock M, Gratwohl A, et al. Rituximab in patients with hairy cell leukemia relapsing after treatment with 2-chlorodeoxyadenosine (SAKK 31/98). Haematologica 2008;93:1426-1428. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18603561.

41. Else M, Dearden CE, Matutes E, et al. Rituximab with pentostatin or cladribine: an effective combination treatment for hairy cell leukemia after disease recurrence. Leuk Lymphoma 2011;52 Suppl 2:75-78. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21504288.

42. Else M, Osuji N, Forconi F, et al. The role of rituximab in combination with pentostatin or cladribine for the treatment of recurrent/refractory hairy cell leukemia. Cancer 2007;110:2240-2247. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17886250.

43. Ravandi F, Jorgensen JL, O'Brien SM, et al. Eradication of minimal residual disease in hairy cell leukemia. Blood 2006;107:4658-4662. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16497968.

44. Ravandi F, O'Brien S, Jorgensen J, et al. Phase 2 study of cladribine followed by rituximab in patients with hairy cell leukemia. Blood 2011;118:3818-3823. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21821712.

45. Gerrie AS, Zypchen LN, Connors JM. Fludarabine and rituximab for relapsed or refractory hairy cell leukemia. Blood 2012;119:1988-1991. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22223825.

46. Kreitman RJ, Stetler-Stevenson M, Margulies I, et al. Phase II trial of recombinant immunotoxin RFB4(dsFv)-PE38 (BL22) in patients with hairy cell leukemia. J Clin Oncol 2009;27:2983-2990. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19414673.

47. Kreitman RJ, Tallman MS, Robak T, et al. Phase I Trial of Anti-CD22 Recombinant Immunotoxin Moxetumomab Pasudotox (CAT-8015 or HA22) in Patients With Hairy Cell Leukemia. J Clin Oncol 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22355053.

48. Genentech, Inc. Prescribing Information: ZELBORAF® (vemurafenib) tablet, oral. 2012. Available at: http://www.gene.com/download/pdf/zelboraf_prescribing.pdf. Accessed May 2013.

49. Dietrich S, Glimm H, Andrulis M, et al. BRAF inhibition in refractory hairy-cell leukemia. N Engl J Med 2012;366:2038-2040. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22621641.

50. Peyrade F, Re D, Ginet C, et al. Low-dose vemurafenib induces complete remission in a case of hairy-cell leukemia with a V600E mutation. Haematologica 2013;98:e20-22. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23300174.

Peripheral T-Cell Lymphomas

Peripheral T-cell lymphomas (PTCL) are a heterogeneous group of lymphoproliferative disorder arising from mature T-cells of post-thymic origin.[1] PTCL represent a relatively uncommon group of hematologic malignancies within non-Hodgkin lymphomas (NHL), accounting for about 10% of NHL cases.[2] The prognosis for PTCL remains poor in comparison to B-cell NHL. This is largely due to lower response rates and less durable responses to standard combination chemotherapy regimens such as CHOP. Progress has been further hampered by the relative rarity and the biological heterogeneity of the diseases. Among PTCL cases worldwide, the most common subtypes include PTCL-not otherwise specified (PTCL-NOS; 26%), angioimmunoblastic T-cell lymphoma (AITL; 18.5%), NK/T-cell lymphoma (10%), adult T-cell leukemia/lymphoma (ATLL; 10%), ALK-positive anaplastic large cell lymphoma (ALCL; 7%) and ALK-negative ALCL (6%); subtypes such as enteropathy-associated T-cell lymphoma (EATL; <5%) and primary cutaneous ALCL are relatively rare (<2%) with ALCL more common than NK/T or ATLL in the United States.[3]

PTCL-NOS is the most common subtype of PTCL. It most often involves nodal sites, however, many patients present with extranodal involvement including the liver, bone marrow, GI tract and skin. PTCL-NOS is associated with poorer overall survival (OS) and event-free survival (EFS) rates compared to B-cell lymphomas.[4-6]

AITL usually presents with generalized lymphadenopathy, often with associated hepatomegaly or splenomegaly, hypergammaglobulinemia, eosinophilia, skin rash and fever. It occurs mainly in older patients. Prognosis is similar to PTCL-NOS. In a single institution study, which reviewed the data from 199 patients with PTCLs, the 5-year OS and PFS rates were 36% and 13%, respectively, for the subgroup of

patients with AITL.[6] In the most recent report from the GELA study, which included the largest series of patients with AITL (n=157), 5- and 7-year OS rates were 33% and 29%, respectively, reaching an apparent plateau around 6 years.[7] The corresponding EFS rates were 29% and 23%, respectively.

ALCL is a CD30-expressing subtype of PTCL which accounts for less than 5% of all cases of NHL. There are now three distinctly recognized subtypes of ALCL: systemic ALK-1 expressing ALCL, systemic ALK-1 negative ALCL, and primary cutaneous ALCL. ALK-positive ALCL is most common in children and young adults. It is characterized by the overexpression of anaplastic lymphoma kinase (ALK-1) protein, which is the result of a chromosomal translocation [t(2;5)] in 40-60% of patients.[8] Systemic ALK-positive ALCL predominantly occurs at younger age and has a good prognosis compared to ALK-negative ALCL, which occurs in older patients. The majority of patients with ALCL present with advanced stage III or IV disease (65% for ALK-positive and 58% for ALK-negative) frequently associated with systemic symptoms and extra nodal involvement.[3] In general ALK-positive ALCL is associated with better clinical outcomes than ALK-negative ALCL, PTCL-NOS or AITL although the favorable prognosis of ALK-1 positivity is diminished with older age and higher prognostic risk scores. Five-year OS rate following anthracycline-based therapy was 79% for ALK-positive ALCL compared to 46% for ALK-negative ALCL.[9] Recent survival analysis from the International T-cell Lymphoma Project also reported similar outcomes.[3,10] The differences in prognosis are most pronounced for younger patients with favorable prognostic factors. In this report, ALK-positive ALCL was associated with significantly better prognosis with anthracycline-containing regimens compared with ALK-negative ALCL, both in terms of the 5-year failure-free survival (FFS) rate (60% vs. 36%; *P*=0.015) and OS rate (70% vs. 49%; *P*=0.016).[10] The 5-year FFS

and OS rates for patients with PTCL-NOS were 20% and 32%, respectively. The 5-year FFS and OS rates for patients with AITL were 18% and 32%, respectively.[3]

Primary cutaneous variant of ALCL is noted for the absence of ALK1 protein and for an indolent disease course characterized by frequent relapses, generally confined to the skin. Primary cutaneous ALCL is associated with long-term survival despite cutaneous relapses. As a result, combination chemotherapy is rarely indicated for these patients. In the aforementioned analysis conducted by the International T-cell Lymphoma Project, the 5-year FFS and OS rates among patients with primary cutaneous ALCL were 55% and 90%, respectively.[3]

During the last decade, numerous reports of primary breast ALCL occurring in association with breast implants have appeared in anecdotal reports and case series. NHL of the breast is rare, comprising only <0.5% of malignant breast tumors and about 2% of extranodal lymphomas.[11-13] The majority of cases of NHL of the breast are of B-cell origin.[11-15] However, in recent years, reports have emerged that suggest an association between breast implants and ALCL of the breast.[11,12,16] In a matched case-control study based on a national pathology registry from the Netherlands, 11 patients with ALCL of the breast were identified over a 17-year time period; pathological and clinical characteristics of these patients were compared with those of control patients (n=30; matched for age and year of diagnosis) with other types of lymphomas in the breast.[16] Five of the patients with breast ALCL had received breast implants while one patient in the control group had received an implant prior to lymphoma diagnosis. The odds ratio for ALCL associated with breast implants was 18 (95% CI, 2-157).[16] Thus, the probability of developing ALCL was higher among women with breast implants compared with those without implants, although the absolute risk remains very low given the rarity of ALCL of the breast.

ALCL associated with breast implants are frequently ALK-negative, and primarily occur within the fibrous capsule around the implant, within the periimplant fluid, as a seroma, or otherwise within the vicinity of the implant.[11,12,16,17] Based on a literature review of the clinical and histological findings of ALK-negative ALCL associated with breast implants, it has been suggested that this lymphoma may represent a distinct entity from systemic ALCL, but may be more similar to primary cutaneous or indolent ALCL in terms of clinical behavior.[11,12] Although the majority of reported cases of ALCL associated with breast implants appear to be limited to localized disease, systemic involvement and death due to ALCL have also been rarely reported.[11,18] These reported cases of aggressive disease appear more common in ALCL of the breast parenchyma rather than of the fibrous capsule or seroma and may represent a different process than has been reported in the majority of the implant associated cases. At the present time it is unclear as to the best management strategy for implant associated ALCL localized to the capsule or seroma. For patients with localized disease it appears that removal of the implant and the capsule are sufficient for many but predictors to identify the infrequent patients with a higher risk for dissemination are not known.[11,17,18]

Given the concern raised by the medical community with regards to breast implants and its putative association with ALK-negative ALCL, the FDA recently conducted a literature-based assessment to better characterize the potential association between implants and ALCL. In the report, the FDA indicated that "women with breast implants may have a very small but increased risk of developing this disease in the scar capsule adjacent to the implant" but that "the totality of evidence continues to support a reasonable assurance that FDA-approved breast implants are safe and effective when used as labeled".[19] At this time,

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the pathogenesis of ALCL associated with breast implants and the causal effect of such implants remain unknown.

EATL is a rare T-cell lymphoma of the small intestine, accounting for <1% of all the NHLs and associated with a very poor prognosis. The median age of diagnosis is 60 years. The typical immunophenotype of EATL is CD3+, CD5–, CD7+, CD8–/+, CD4– and CD103+. Anthracycline-based chemotherapy with CHOP or CHOP-like regimens is most commonly used for patients with EATL[20-23]; however, outcomes remain poor with these conventional therapeutic approaches. In the aforementioned analysis from the International T-cell Lymphoma Project, the 5-year FFS and OS rates in patients with EATL primarily treated with anthracycline-based regimens were 4% and 20%, respectively.[3] Recent studies have shown that more intensive regimens followed by high-dose therapy followed by autologous stem cell rescue (HDT/ASCR) may improve outcomes in patients with EATL.[24-26]

Staging and Prognosis

Staging is similar to that of the other aggressive lymphomas. Historically, the International Prognostic Index (IPI) derived for DLBCLs has been used and was shown to have prognostic value for patients with PTCL. In 2004, the Italian Intergroup for lymphoma proposed a new prognostic index for PTCL-NOS.[4] Risk factors identified based on multivariate analysis included the following: age older than 60 years, elevated LDH levels, performance status of 2 or more, and bone marrow involvement. Five-year OS rate was only 33% for patients with 2 risk factors and 18% for those with 3 or 4 risk factors. This schema also identified a subset of patients with relatively favorable prognosis, who had adverse risk factors.[4] This group represented 20% of patients and had a 5-year OS rate of 62%. In the NCCN Guidelines, patients with stage I-II disease are stratified into 2 groups (low intermediate risk

and high intermediate risk) based on the age-adjusted International Prognostic Index (aaIPI).

In a retrospective GELA study, the prognosis of patients with PTCL (including all subgroups) were compared with patients with B-cell lymphoma with similar characteristics receiving similar aggressive combination chemotherapy, and in some patients, receiving HDT/ASCR.[5] The CR rates were 63% and 54% for patients with B-cell lymphoma and PTCL, respectively. The 5-year event-free survival (EFS) rates were 45% and 32%, respectively. The 5-year OS rate was also higher for patients with B-cell lymphomas compared with patients with PTCL (52% vs. 41%). The difference in 5-year OS rates between B-cell lymphomas and PTCL were most pronounced in patients with 2 or 3 adverse risk factors as determined by IPI (53% vs. 36% for 2 risk factors; and 35% vs. 23% for 3 risk factors).[5] Initial characteristics and prognostic features were analyzed in another retrospective study in 174 patients with PTCL. Most patients were treated with anthracycline-based regimens.[27] The complete response (CR) rates (69% vs. 45%) and median survival (65 months vs. 20 months) were better for ALCL subgroup compared to other PTCL subtypes.

Diagnosis

Diagnosis of PTCL is similar to that described for other lymphomas, requiring adequate immunophenotyping to distinguish PTCL from B-cell neoplasms. The initial paraffin panel for immunohistochemistry (IHC) studies may only include pan-T-cell markers and can be expanded to include antibodies of T-cell lymphoma, if suspected. The following markers should be considered for the IHC analysis: CD2, CD3, CD5, CD7, CD4, CD8, CD30, CD56, CD57, CD10, CD20, CD21, CD23, ALK, EBER-ISH, BCL6, and Ki-67. Alternatively, the following markers can be analyzed by flow cytometry: CD2, CD3, CD5, CD7, CD4, CD8, CD30,

CD10, CD19, CD20, CD45, kappa/lambda, TCRαβ, and TCRγ. Additional IHC studies to evaluate βF1, CD279/PD1, and CXCL-13 may be useful under certain cases to establish lymphoma subtype. PTCL is often associated with clonal rearrangements of the T-cell receptor (TCR) genes that are less frequently seen in non-cancer T-cell diseases, although false positive results or non-malignant clones can at times be identified. Under certain circumstances, molecular analysis to detect *TCR* gene rearrangements and translocations involving the *ALK* gene, i.e., t(2;5) or variant, may be useful.

PTCL-NOS has variable T-cell associated antigens and usually lacks B-cell associated antigens (although aberrant CD20 expression in T-cell lymphomas is infrequently encountered). With the exception of CD30 expression in ALCL, antigen expression is variable across the aggressive T-cell lymphomas. The majority of the nodal cases express CD4+ and lack CD8-, however CD4-/CD8+, CD4-/CD8-, and CD4+/CD8+ cases are seen.[28] While CD30 expression can be found at times in many T-cell lymphomas, systemic ALCL has uniform strong expression of CD30. In ALCL cases only, evaluation of ALK1 status, either based on immunophenotyping or genetic analysis of the t(2;5) or variant chromosomal rearrangements, is important to identify the ALK1 positive tumors that have a better prognosis. AITL cells express T-cell associated antigens and are usually CD4+. Expression of CXCL13 has been identified as a useful marker that may help distinguish AITL from PTCL-NOS.[29,30] It is also characterized by the frequent presence of Epstein-Barr virus (EBV)-positive B-cells and cases of co-existent EBV+DLBCL are reported. EBER (EBV-encoded RNA) is positive in about 40% of PTCL and some case series have reported that EBER positive tumors have a worse prognosis.

Workup

The workup for PTCL is similar to the workup for other lymphoid neoplasms. The workup focuses on determining the stage of the disease based on routine laboratory studies (CBC with differential and platelets, comprehensive metabolic panel), physical examination including a full skin exam, and imaging studies, as indicated. CT scan with diagnostic quality and/or PET-CT scan of the chest, abdomen, and pelvis are essential during workup. In some cases, CT scan of the neck and CT or MRI of the head may be useful. MUGA scan or echocardiogram is also recommended, since chemotherapy is usually anthracycline based. In selected cases, serology testing for HIV and HTLV-1 (human T-cell lymphoma virus) may be useful. HTLV-1 positivity, in particular, can lead to the alternate diagnosis and alternate management of ATLL for cases that would otherwise be classified as PTCL-NOS by the pathologist if positive HTLV-1 serology was not known.

Treatment Options

Induction Therapy
PTCLs are less responsive to and have less frequent durable remissions with standard chemotherapy regimens such as CHOP and thus carry a poorer prognosis compared to diffuse large B-cell lymphomas. In prospective randomized studies, PTCLs have been included with aggressive B-cell lymphomas.[31,32] However, it has not been possible to assess the impact of chemotherapy in this subgroup of patients with PTCLs due to small sample size. Only limited data exist from randomized trials comparing the efficacy of chemotherapy regimens exclusively in patients with PTCL.[33]

CHOP chemotherapy is the most commonly used first-line regimen for patients with PTCL. However, with the exception of ALK+ ALCL,

outcomes are disappointing compared to the favorable results achieved with DLBCL. Chemotherapy regimens that are more intensive than CHOP have not shown any significant improvement in OS in patients with PTCL, with the exception of ALCL.[34,35]

CHOP chemotherapy is frequently curative in only the small number of patients with favorable prognostic features.[3,10] As previously discussed, retrospective analysis from the International T-cell Lymphoma Project showed that anthracycline-based chemotherapy did not favorably impact survival in patients with the most common forms of PTCLs, namely PTCL-NOS and AITL.[3] In a retrospective study conducted by the British Columbia cancer agency, the 5-year OS rate for patients with PTCL-NOS primarily treated with CHOP or CHOP-like regimens was only 35%; among these patients, the 5-year OS rates were higher in patients with low-risk IPI scores compared with those with high-risk IPI scores (64% vs. 22%, respectively).[6] In addition, patients with ALK-positive ALCL had superior clinical outcome compared to those with ALK-negative ALCL (5-year OS 58% vs. 34%, respectively). The addition of etoposide to CHOP (CHOEP regimen) compared with CHOP alone was evaluated in a randomized study by the German High-grade NHL Study Group (DSHNHL). In relatively young patients with favorable prognosis aggressive NHL (age ≤60 years; normal LDH levels), the CHOEP regimen resulted in significantly higher CR rate (88% vs. 79%; P=0.003) and 5-year EFS rate (69% vs. 58%; P=0.004).[36] No difference was observed in OS outcomes between the regimens. It should also be noted that in this study, the majority of patients had B-cell histology, with only 14% diagnosed with T-cell NHL (with 12% of patients having ALCL, PTCL-NOS, or AITL histology).[36] In an analysis of a large cohort of patients with PTCL treated within the DSHNHL trials, patients with ALK-positive ALCL had favorable outcomes with CHOP or CHOP with etoposide (CHOEP).[35] Three-year EFS and OS rates were 76% and

90%, respectively, for patients with ALK-positive ALCL. The corresponding outcomes were 50% and 67.5%, respectively, for AITL, 46% and 62%, respectively, for ALK-negative ALCL and 41% and 54%, respectively, for PTCL-NOS. Among those with T-cell lymphoma, CHOEP was associated with a trend for improved EFS among relatively young patients (age <60 years) and is an option for these patients. CHOP-21 appeared to be the standard regimen for patients age >60 years, given that the addition of etoposide did not provide an advantage in these older patients due to increased toxicity. Among patients with ALK-negative ALCL, AITL and PTCL-NOS, those with low-risk IPI scores (IPI <1) had a relatively favorable prognosis; contrastingly, patients with higher risk IPI scores derived minimal benefit from CHOP or CHOEP.[35]

Intensive chemotherapy regimens have also been evaluated in the treatment of patients with PTCL. In a retrospective analysis of data from patients with T-cell malignancies treated at the MD Anderson Cancer Center (N=135; PTCL-NOS, n=50; ALCL, n=40; AITL, n=14), outcome with CHOP was compared with outcomes with more intensive chemotherapy regimens, one of which included a regimen with hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and prednisone (hyper-CVAD).[34] The estimated median OS was 46 months for all patients. The 3-year OS rate with CHOP and intensive therapies was 62% and 56%, respectively. Within the subgroup of patients with ALCL, those with ALK-positive disease showed a trend for a higher 3-year OS rate compared with those with ALK-negative ALCL (100% vs. 70%, respectively).[34] When the subgroup with ALCL was excluded from the analysis, the median OS was 21 months; the 3-year OS rate with CHOP and intensive therapies was 43% and 49%, respectively.[34] A combination chemotherapy regimen with etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (EPOCH) was first

evaluated by NCI investigators in patients with relapsed/refractory NHL,[37] and this regimen was recently evaluated in patients with previously untreated disease. In a prospective study that evaluated dose-adjusted EPOCH in previously untreated patients with PTCL (N=38; ALK-positive ALCL, n=15; ALK-negative ALCL, n=7; other PTCL, n=16), similar outcomes were reported for ALK-positive and ALK-negative ALCL.[38] The 5-year PFS rates in these subgroups were 80% and 71%, respectively; the 5-year OS was 86% in both groups. Outcomes for non-ALCL subtypes (PTCL-NOS, n=10; AITL, n=1; EATL, n=1; other, n=4) were poorer, with a 5-year PFS and OS of only 32% and 50%, respectively.[38] These results are encouraging for patients with ALCL, but outcomes with chemotherapy regimens remain suboptimal for those with non-ALCL subtypes.

The generally poor results with conventional chemotherapy have led many to explore the role of HDT/ASCR as a first-line consolidation therapy option. Several retrospective studies[39-47] have reported positive outcomes with HDT/ASCR in patients with PTCL. The 3-year OS rate in retrospective studies ranged from 53% to 58% in patients undergoing HDT/ASCT during first-line or subsequent lines of therapy; the 3-year PFS rate correlated with OS outcomes, and ranged from 44% to 50%.[39,47,48] Patients with the AITL subtype generally have poor outcomes, and HDT/ASCR may offer a feasible option for these patients, particularly in the setting of first remission.[42,45,49] In an analysis of data from a large cohort of patients with AITL from the EBMT Lymphoma Registry (N=146), the 2-year and 4-year OS rates overall for patients undergoing HDT/ASCR were 67% and 59%, respectively.[42] For the subgroup of patients who underwent HDT/ASCR in first CR, the 2-year and 4-year OS rates were 81% and 78%, respectively. These data point to the potential promising role of HDT/ASCR for patients with AITL in first CR.

Prospective studies have also demonstrated the potential role of HDT/ASCR in improving treatment outcome in patients with PTCL.[25,50-55] The Nordic lymphoma group evaluated dose-dense induction therapy with CHOEP followed by HDT/ASCR in patients with previously untreated PTCL responding to initial induction (NLG-T-01 study).[25,54,56] Patients with ALK-positive ALCL were excluded from this study. Among 160 patients enrolled with histopathologically confirmed PTCL (PTCL-NOS, 39%; ALK-negative ALCL, 19%; AITL, 19%; EATL, 13%), 115 patients (72%) underwent HDT/ASCR.[25] With a median followup of 60.5 months, the 5-year OS and PFS rates were 51% and 44%, respectively. Treatment-related mortality (TRM) was 4%. The 5-year OS and PFS for the subgroup of patients with PTCL-NOS was 47% and 38%, respectively. Among the subgroup of patients with ALK-negative ALCL, the corresponding rates were 70% and 61%, respectively.[25] In the prospective study conducted by the GELTAMO Study group (N=26), patients with CR or PR to induction therapy with MegaCHOP were planned for ASCR.[50] The 3-year OS and PFS rates on an intent-to-treat basis were 73% and 53%, respectively. At 2-year post-transplant follow-up, OS and PFS rates were 84% and 56%, respectively, among the patients who proceeded to ASCR consolidation (n=19).[50] In a phase II study (N=41), newly diagnosed patients with PTCL responding to high-dose CHOP regimen alternating with etoposide, cisplatin, cytarabine and prednisone, were planned for ASCR.[52] With a median follow-up of 3.2 years, the 4-year OS and PFS rates were 39% and 30%, respectively.

Reimer et al reported the final analysis of the first prospective PTCL-restricted multicenter study on upfront HDT/ASCR in 83 patients.[53] The treatment regimen consisted of four to six cycles of CHOP followed by HDT/ASCR. The ORR following CHOP chemotherapy was 79% (39% CR). Fifty-five of the 83 patients (66%)

received transplantation; the remaining 34% of patients were unable to proceed to transplant, primarily due to progressive disease. After HDT/ASCR, 48 of the 55 patients achieved a CR, and 7 patients achieved a PR. In an intent-to-treat analysis, the ORR after myeloablative therapy was 66% (56% CR). The estimated 3-year OS and PFS rates were 48% and 36%, respectively.[53]. Aggressive chemotherapy with CHOP followed by IVE/MTX (ifosfamide, etoposide and epirubicin alternating with intermediate-dose methotrexate) and HDT/ASCR has been evaluated as initial therapy with positive outcomes in patients with PTCL (N=57).[55] Among these patients, 33 proceeded to ASCR. Based on intent-to-treat analysis, the 3-year OS and PFS rates were 67% and 59%, respectively, for all patients.[55] An ongoing international randomized phase III trial is evaluating the role of adding the CD52 monoclonal antibody alemtuzumab (studies with alemtuzumab are discussed below under relapsed/refractory disease) to CHOP induction (versus CHOP alone; standard arm) in patients with previously untreated PTCL (ACT trial).[57] Patients with ALCL were excluded regardless of ALK status. Patients age 60 years or younger were eligible to proceed with HDT/ASCR (ACT-1). Results from the planned interim analysis of the younger ACT-1 patient group (n=68) reported 1-year EFS of 55%. The 1-year OS and PFS rates were 78% and 54%, respectively. Viral infectious events were more frequent in the alemtuzumab arm (28% vs. 10%), primarily due to asymptomatic cytomegalovirus (CMV) reactivations. The frequency of grade 3 or higher bacterial and fungal infections were similar between treatment arms.[57]

The outcome of ALK-positive ALCL patients undergoing ASCR compared to those with other histological subtype of PTCL was reported in only one prospective study by Corradini et al.[51] The pooled results from two prospective studies (N=62) showed that at a median follow-up of 76 months, the estimated 12-year OS and EFS rates were 34 and 30%, respectively, for the whole study cohort. Overall treatment-related mortality rate was 5%. The 10-year OS and EFS rates were significantly higher among the patients with ALK-positive ALCL (63% and 54%, respectively) compared with patients with other PTCL subtypes (21% and 19%, respectively). In the subgroup of patients with PTCL-NOS, the corresponding survival rates were 37% and 25%, respectively.[51] In a multivariate analysis, the achievement of CR before transplant was a strong predictor of survival benefit. The projected 10-year OS and EFS rates for patients in CR before transplant were 48% and 47%, respectively, compared with 22% and 11%, respectively, for those who were not in CR prior to transplant.[51]

Longer follow-up and preferably a randomized trial, is necessary to evaluate the impact of first-line consolidation therapy on time-to-treatment failure and OS outcomes. In the absence of randomized trials comparing conventional chemotherapy to first-line consolidation with HDT/ASCR, this is a reasonable treatment option only in patients showing good response to induction therapy.

NCCN Recommendations
For patients with ALK-positive ALCL, multiagent chemotherapy (typically CHOP-21 or CHOEP-21) for 6 cycles with or without radiation therapy (RT; an option for stage I-IV disease) or for 3 to 4 cycles with RT (an option in patients with stage I-II disease) is considered standard first-line therapy. Although CHOP or CHOEP regimens are associated with a favorable prognosis in patients with ALK-positive ALCL, these regimens have not resulted in similarly favorable outcomes for patients with other PTCL histologies. Thus, for patients with other subtypes, participation in clinical trials is the preferred management approach. In the absence of suitable clinical trials, multiagent chemotherapy (4-6 cycles) with adjuvant locoregional RT to involved region is

recommended for patients with stage I-II disease (low/low-intermediate risk); patients with higher risk stage I-II (high/high-intermediate risk) or stage III-IV disease are treated with multiagent chemotherapy (6-8 cycles) with or without RT. Suggested multiagent chemotherapy regimens include CHOEP, CHOP-14, CHOP-21, CHOP followed by ICE or IVE, dose-adjusted EPOCH, or hyper-CVAD.

AITL is a highly heterogeneous disease and can at times be treated solely with corticosteroids or other immunosuppressive agents. Cyclosporine has been effective in patients with relapsed disease following treatment with steroid or multiagent chemotherapy.[58] These milder or alternate approaches are often most appropriate for the elderly or those felt to be unlikely to tolerate a combination chemotherapy approach. Most patients with AITL are managed similarly to other forms of PTCL as above; however the NCCN Guidelines panel suggests a trial of singe-agent corticosteroid for symptom management in elderly patients or in patients with comorbid conditions in whom the risks of combination chemotherapy are excessive.

Breast implant-associated ALCL is an emerging clinical entity with unknown origin, and requires individualized care. The aforementioned recommendations do not apply to these cases, as the standard of care has not been established for patients with implant-associated ALCL. Most patients have been managed by removal of the implant and capsule, and in some cases, with chemotherapy with or without RT.[11,19] It is generally recommended that upon confirmation of ALCL diagnosis, both the implant and capsule should be removed from the affected breast. Decisions to remove the unaffected implant or to treat with chemotherapy and/or RT should be made on an individual basis according to the extent of disease involvement.

Follow-up Therapy

All patients (except for those with ALK-positive ALCL) undergo interim restaging following initial therapy by repeating all prior positive studies. If a PET-CT scan is positive, rebiopsy is recommended before changing course of treatment. Patients are then divided into three groups according to treatment response (CR, PR or no response or progressive disease). Subsequent treatment options depend on whether the patient initially presented with Stage I-II or Stage III-IV disease.

Stage I or II disease (aaIPI low/low-intermediate)

In patients showing CR after interim restaging, planned RT is completed. RT or HDT/ASCR with or without RT is considered for patients showing PR at interim staging. Clinical trials including allogeneic transplant or RT is another option for this group of patients. End-of-treatment restaging is performed after completion of treatment. No further treatment is necessary for those showing CR; these patients can be monitored by follow up every 3-6 months for 5 years, and then yearly as clinically indicated. Patients with PR at end-of-treatment restaging and those with no response or progressive disease following initial or follow-up therapy are treated as described for relapsed or refractory disease.

Stage I or II disease (aaIPI high-intermediate/high) or stage III-IV

Patients with a CR can be observed or can be consolidated with HDT/ASCR. Local RT can be given prior to or following HDT. Patients with PR or no response or progressive disease after initial therapy are treated similarly to patients with relapsed or refractory disease.

Treatment for Relapsed or Refractory Disease

Several retrospective studies have evaluated the role of HDT/ASCR in patients with relapsed or refractory PTCL.[44,59-63] In patients with relapsed or primary refractory PTCL (N=36) undergoing HDT/ASCR,

the 3-year EFS and OS rates were 37% and 48%, respectively, which appeared similar to outcomes of patients with relapsed diffuse large B-cell lymphoma (DLBCL) who received HDT/ASCR in a retrospective comparison (42% and 53%, respectively).[62] In another retrospective study of patients with relapsed or primary refractory PTCL (N=24; excluding patients with ALK-positive ALCL) who received HDT/ASCR, the 5-year PFS and OS rates were 24% and 33%, respectively; these outcomes also appeared similar to outcomes in patients with relapsed DLBCL (34% and 39%, respectively).[60] Aggressive second-line chemotherapy with ICE followed by HDT/ASCR was evaluated in patients with relapsed/refractory PTCL.[59] Among 40 patients treated with ICE, 27 (68%) underwent HDT/ASCR. Based on intent-to-treat analysis, median PFS was 6 months from the time of last ICE therapy; 70% of patients relapsed within 1 year. Patients with relapsed disease had significantly higher 3-year PFS rate compared with those who were primary refractory (20% vs. 6%; *P*=0.0005).[59] Nevertheless, salvage therapy for patients with relapsed/refractory PTCL remains suboptimal, even with the incorporation of HDT/ASCR. In a retrospective review of patients with PTCL who underwent HDT/ASCR at Stanford University (N=53), the 5-year PFS rates for patients in first CR/PR, CR/PR after second-line therapy and those with refractory disease were 51%, 12%, and 0%, respectively; the 5-year OS rates were 76%, 40%, and 30%, respectively.[63] The disease status and the number of prior regimens received prior to transplant were significant prognostic factors. In a retrospective analysis of data from the Spanish Group for Lymphoma and Autologous Transplantation (GEL-TAMO) registry (N=115), the 5-year OS rate was 45% for the group of patients with PTCL treated with HDT/ASCR in the salvage setting (n=78) compared with 80% for those who were transplanted in first CR (n=37) (*P*=0.007).[61] Within the group of patients in the salvage setting, the 5-year OS rates for patients who underwent HDT/ASCR in first PR, CR at second-line or later lines of

therapy, or with refractory disease, were 46%, 54%, and 0%, respectively.[61] In an analysis of data from CIBMTR that evaluated outcomes with HDT/ASCR and allogeneic stem cell transplantation (SCT) in patients with T-cell lymphomas (N=241; ALCL, 46%; PTCL, 42%), HDT/ASCR resulted in improved outcomes compared with allogeneic SCT for the subgroup of patients with ALCL histology but not for other histologies.[64] Among patients with ALCL (n=111), HDT/ASCR resulted in significantly higher 3-year PFS (55% vs. 35%; *P*=0.03) and OS (68% vs. 41%; *P*=0.003) compared with allogeneic SCT. Survival outcomes with HDT/ASCT appeared less favorable for patients with PTCL-NOS (n=102), and no significant differences in outcomes were observed between HDT/ASCR and allogeneic SCT with regards to 3-year PFS (29% vs. 33%) or OS (45% vs. 42%) in this subgroup.[64] For patients who received transplantation beyond first CR, HDT/ASCR resulted in numerically higher 3-year PFS (41% vs. 33%) and OS (53% vs. 41%) compared with allogeneic SCT, but these differences were not statistically significant; cumulative incidence of non-relapse mortality was higher with allogeneic SCT compared with HDT/ASCR in patients transplanted beyond first CR (*P*<0.001).[64] Thus, these findings suggest that HDT/ASCR as first-line consolidation therapy may be associated with a durable survival benefit, while this treatment modality only infrequently results in durable benefit in patients with relapsed or refractory disease—possibly with the exception of patients with relapsed ALCL. Additional data are awaited from the CIBMTR analysis.

Recent reports have shown that allogeneic SCT may provide an option for patients with relapsed or refractory PTCL. In a retrospective analysis of data from the French registry for patients who received allogeneic SCT (N=77; PTCL-NOS 35%; ALCL 35%; AITL 14%), the 5-year EFS and OS rates were 53% and 57%, respectively.[65] The 5-year transplant-related mortality (TRM) rate was 34%; TRM at 100 days was 21%.

Patients had previously received a median of 2 prior therapies (range, 1-5), and 74% had received myeloablative conditioning prior to transplantation.[65] Patients who received ≤2 lines of prior chemotherapy had significantly higher 5-year OS rate compared with those who received >2 lines (73% vs. 39%; *P*=0.003). The 5-year OS rate was also significantly higher among patients transplanted in remission (CR or PR) compared with those who were transplanted with less than a PR (69% vs. 29%; *P*=0.0003). No significant differences in outcomes (OS, EFS, or TRM) were observed between types of conditioning regimen. Based on multivariate analysis, resistant disease (less than PR) at the time of transplantation and severe acute graft-versus-host disease (GVHD) were significant independent predictors for worse survival outcomes.[65] In the aforementioned analysis of data from the CIBMTR database for patients with T-cell lymphomas undergoing transplantation (N=241; PTCL, 42%), outcomes with HDT/ACSR (n=115) and allogeneic SCT (n=126; myeloablative conditioning in 59%) were reported.[64] A higher percentage of patients undergoing HDT/ASCR had ALCL histology, chemosensitive disease, and were transplanted in first CR, compared with patients undergoing allogeneic SCT. The TRM rate at 100 days was 2% for the HDT/ASCR group compared with 17% for the allogeneic SCT group. For the group of patients who were transplanted in the salvage setting (i.e., less than first CR), the 3-year OS rate was 53% with HDT/ASCR compared with 41% with allogeneic SCT.[64] In a recent analysis of single-institution data from the M.D. Anderson Cancer Center, outcomes were reported for patients with T-cell lymphomas (N=196; PTCL-NOS, n=61; ALCL, n=50; AITL, n=19) who underwent HDT/ASCR (n=119) or allogeneic SCT (n=77; myeloablative conditioning in 75%).[66] Among the patients who underwent HDT/ASCR, PFS and OS rates were 30% and 39%, respectively, after a median follow up of 39 months. Among the patients who underwent allogeneic SCT, the PFS and OS rates were 30% and

43%, respectively, after a median follow up of 65 months. Among the subgroup of patients in the allogeneic SCT group who had nodal T-cell lymphoma (PTCL-NOS, ALCL, or AITL), the 3-year PFS and OS rates were 23% and 38%, respectively. The patients in this latter subgroup were primarily (87%) transplanted in the salvage setting (i.e., less than first CR).[66] Collectively, these findings from retrospective analyses of data point to a 3-year OS rate of about 40% in patients who undergo allogeneic SCT (primarily with myeloablative conditioning) for relapsed or refractory PTCL. However, the early TRM rates are high with this procedure, with a reported 100-day TRM rate of about 20%.

Other studies have evaluated the role of allogeneic SCT using reduced intensity conditioning (RIC) in patients with relapsed/refractory PTCL. In a phase II study, Corradini et al investigated the role of RIC allogeneic SCT in patients with relapsed or refractory PTCL (N=17).[67] The estimated 3-year PFS and OS rates were 64% and 81%, respectively. Donor lymphocyte infusion induced responses in some patients progressing after allografting. The estimated probability of non-relapse mortality (NRM) at 2 years was 6%.[67] A recent study reporting on retrospective analysis of long-term data from patients with relapsed/refractory PTCL treated with RIC allogeneic SCT (N=52; PTCL-NOS, n=23; ALCL, n=11; AITL, n=9) showed 5-year PFS and OS rates of 40% and 50%, respectively.[68] The 5-year NRM rate was 12%, and extensive chronic GVHD was associated with increased risks for NRM. The 5-year cumulative relapse rate was 49%; worse disease status at the time of transplantation and greater lines of prior therapy were associated with higher relapse risks.[68] A retrospective study of data from the EBMT database demonstrated that allogeneic SCT induced long-term remissions in patients with AITL (N=45; 62% of patients had ≥2 lines of therapy prior to transplantation) .[69] Myeloablative conditioning was employed in 56% of patients while the

remaining patients received RIC. The cumulative NRM rate at 1 year was 25%; these rates were similar between myeloablative conditioning (29%) and RIC (24%). The estimated 3-year relapse rate was 20%. The 3-year PFS and OS rates were 54% and 64%, respectively. These outcomes were not significantly different between conditioning regimens.[69] Patients with chemotherapy-sensitive disease had a significantly higher rate PFS compared with those with refractory disease (66% vs. 33%, respectively). Further prospective data are needed to determine the role of allogeneic SCT (either with myeloablative conditioning or RIC) in patients with relapsed/refractory PTCL.

Until recently, data to guide the treatment of patients with relapsed and refractory PTCL came from small series of patients treated with various single agents. Many of the drugs used are extrapolated from the following reports; gemcitabine[70-72] and alemtuzumab [73,74] have shown for activity in such experiences. Zinzani et al recently reported the outcome of patients with relapsed/refractory T-cell lymphoma (N=39) treated with gemcitabine (on days 1, 8, and 15 on a 28-day schedule; 1200 mg/m/day for a total of three to six cycles). Among the subgroup of 20 patients with PTCL-NOS, the ORR was 55% (CR 30%); 5 of these patients were in continuous CR with a median duration of CR of 34 months (range, 15-60 months).[72] In a pilot study, alemtuzumab at standard dose schedule produced an ORR of 36% (CR 21%) among patients with relapsed or chemotherapy-refractory PTCLs (N=14).[73] However, alemtuzumab therapy was associated with significant hematologic toxicity and infectious complications, including 5 deaths due to opportunistic infections.[73] The preliminary results of another phase II study showed that in patients with pretreated T-cell lymphoma (N=10; PTCL, n=6), alemtuzumab at a reduced dose was less toxic and as equally effective as the standard dose used in the prior pilot study.[74]

The ORR was 60% (CR 20%). In the subset of patients with PTCL-NOS, ORR was 50% (CR 33%). CMV reactivation was observed only in 10% of patients, as compared with 42% of the patients reported by Enblad et al. The median duration of response was 7 months.[74]

Pralatrexate is a new antifolate with a high affinity for reduced folate carrier type 1 (RFC-1), and has shown significant activity in patients with relapsed/refractory T-cell lymphoma.[75-77] Results from the pivotal, international, phase II study (PROPEL) showed that pralatrexate resulted in an ORR of 29% (CR 11%; response assessed by an independent central review) in pretreated patients with relapsed or refractory PTCL (N=109 evaluable).[76,78] Patients on this study had received a median of 3 prior systemic therapies (range, 1-12); moreover, 63% were refractory to their most recent prior therapy, 24% had never responded to any prior therapy, and 16% had received prior autologous SCT. The median duration of response was 10 months. For all patients, the median PFS and OS were 3.5 months and 14.5 months, respectively.[76] The most common grade 3-4 adverse events included thrombocytopenia (32%), neutropenia (22%), anemia (18%), and mucositis (22%).[76] In September 2009, , pralatrexate became the first FDA-approved single agent for the treatment of patients with relapsed or refractory PTCL.

Romidepsin is a histone deacetylase (HDAC) inhibitor with single-agent activity in patients with relapsed or refractory CTCL and PTCL. In the pivotal multicenter phase II study, romidepsin induced responses in patients with relapsed/refractory PTCL (N=130 evaluable).[79,80] Patients on this study had received a median of 2 prior systemic therapies (range, 1-8), and 16% had failed prior autologous HSCT. The ORR was 25% (CR/CRu 15%; response evaluated by an independent review committee); the ORR and CR/CRu rate by investigator assessment was 39% and 16%, respectively.[80] Median duration of response was 17

months. The median PFS for all patients was 4 months; median PFS for patients with a CR/CRu was 18 months. The most common grade ≥3 adverse events included thrombocytopenia (24%), neutropenia (20%), and infections (19% for any; including pneumonia [5%] and sepsis [5%]).[79,80] In another multicenter phase II study, romidepsin was evaluated in patients with previously treated PTCL (N=47; PTCL-NOS, 57%; AITL, 15%; ALCL, 8.5%).[81] Patients had received a median of 3 prior therapies (range, 1-11), including SCT in 38% of patients. The ORR was 38% (CR 18%) and the median duration of response was 8.9 months. Among responding patients, the median time to progression was 13 months.[81] Romidepsin was approved by the FDA in June 2011 for the treatment of patients with relapsed PTCL.

Brentuximab vedotin is an antibody-drug conjugate that targets CD30-expressing malignant cells by binding to CD30 on the cell surface. After internalization, a potent antimicrotubule agent (monomethyl auristatin E) is released within the cell.[82,83] A multicenter phase II study evaluated brentuximab vedotin (IV 1.8 mg/kg every 3 weeks, up to 16 cycles) in patients with relapsed or refractory systemic ALCL (N=58). Patients had received a median of 2 prior systemic therapies (range, 1–6) and 62% were considered to have primary refractory disease; in addition, 50% of patients were refractory to their most recent prior therapy and 22% had never responded to any therapy.[84] The ORR was 86% (evaluated by an independent review committee) with CR in 57% of patients. The median duration of response was approximately 13 months. The median PFS for all patients was 13 months; the median OS has not been reached with current follow up.[84] The most common grade 3 or 4 adverse events reported in this study included neutropenia (21%), thrombocytopenia (14%), and peripheral sensory neuropathy (12%).[84] No treatment-related deaths were reported. Based upon the results from this study, brentuximab vedotin was approved by the FDA (August 2011) for

treating patients with systemic ALCL after failure of at least one prior multiagent chemotherapy regimen. This agent has not been evaluated in patients with relapsed/refractory cutaneous ALCL and therefore cannot be recommended for those patients at this time.

Bendamustine is an alkylating agent with a purine-like benzimidazole ring component, and is currently indicated for the treatment of patients with indolent NHL refractory to prior rituximab-containing regimen, and those with chronic lymphocytic leukemia (CLL). This agent was recently evaluated in a multicenter phase II study (BENTLEY trial) in patients with relapsed or refractory PTCL (N=60; AITL, 53%; PTCL-NOS, 38%).[85] Patients had received a median of 1 prior therapy (range, 1–3) and 45% were considered refractory to their last therapy; 92% had received prior CHOP or CHOP-like regimens. The ORR after 3 cycles of bendamustine was 50% with CR (including CRu) in 28% of patients. Forty patients (67%) had completed 3 or more cycles of bendamustine; 25% received all 6 cycles of therapy. The median duration of response was short, at only 3.5 months.[85] The median PFS and OS for all patients was 3.6 months and 6.3 months, respectively. The most common grade 3 or 4 toxicity included neutropenia (30%), thrombocytopenia (24%), and infectious events (20%).[85]

NCCN Recommendations

Patients who are candidates for transplant can be treated with second-line chemotherapy prior to transplant. Consolidation therapy with HDT/ASCR or allogeneic HSCT is recommended for those with a CR or PR. Localized areas can be treated with RT before or after high-dose therapy. Patients who are not candidates for transplant are treated with second-line regimens or palliative RT. Suggested treatments include alemtuzumab, bortezomib, brentuximab vedotin (for patients with systemic ALCL only), cyclosporine (for patients with refractory AITL only), dose-adjusted EPOCH, gemcitabine, pralatrexate,

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or romidepsin. Participation in a clinical trial is strongly preferred for these patients. In patients receiving romidepsin, serum potassium and magnesium levels should be monitored to minimize any risk of ECG abnormalities.

Discussion update in progress

References

1. Savage KJ. Peripheral T-cell lymphomas. Blood Rev 2007;21:201-216. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17512649.

2. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 1997;89:3909-3918. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9166827.

3. Vose J, Armitage J, Weisenburger D. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol 2008;26:4124-4130. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18626005.

4. Gallamini A, Stelitano C, Calvi R, et al. Peripheral T-cell lymphoma unspecified (PTCL-U): a new prognostic model from a retrospective multicentric clinical study. Blood 2004;103:2474-2479. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14645001.

5. Gisselbrecht C, Gaulard P, Lepage E, et al. Prognostic significance of T-cell phenotype in aggressive non-Hodgkin's lymphomas. Groupe d'Etudes des Lymphomes de l'Adulte (GELA). Blood 1998;92:76-82. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9639502.

6. Savage KJ, Chhanabhai M, Gascoyne RD, Connors JM. Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification. Ann Oncol 2004;15:1467-1475. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15367405.

7. Mourad N, Mounier N, Briere J, et al. Clinical, biologic, and pathologic features in 157 patients with angioimmunoblastic T-cell lymphoma treated within the Groupe d'Etude des Lymphomes de l'Adulte (GELA) trials. Blood 2008;111:4463-4470. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18292286.

8. Falini B, Pileri S, Zinzani PL, et al. ALK+ lymphoma: clinico-pathological findings and outcome. Blood 1999;93:2697-2706. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10194450.

9. Gascoyne RD, Aoun P, Wu D, et al. Prognostic significance of anaplastic lymphoma kinase (ALK) protein expression in adults with anaplastic large cell lymphoma. Blood 1999;93:3913-3921. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10339500.

10. Savage KJ, Harris NL, Vose JM, et al. ALK- anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. Blood 2008;111:5496-5504. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18385450.

11. Lazzeri D, Agostini T, Bocci G, et al. ALK-1-negative anaplastic large cell lymphoma associated with breast implants: a new clinical entity. Clin Breast Cancer 2011;11:283-296. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21729665.

12. Roden AC, Macon WR, Keeney GL, et al. Seroma-associated primary anaplastic large-cell lymphoma adjacent to breast implants: an indolent T-cell lymphoproliferative disorder. Mod Pathol 2008;21:455-463. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18223553.

13. Talwalkar SS, Miranda RN, Valbuena JR, et al. Lymphomas involving the breast: a study of 106 cases comparing localized and disseminated neoplasms. Am J Surg Pathol 2008;32:1299-1309. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18636016.

14. Cohen PL, Brooks JJ. Lymphomas of the breast. A clinicopathologic and immunohistochemical study of primary and secondary cases. Cancer 1991;67:1359-1369. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1991299.

15. Validire P, Capovilla M, Asselain B, et al. Primary breast non-Hodgkin's lymphoma: a large single center study of initial

characteristics, natural history, and prognostic factors. Am J Hematol 2009;84:133-139. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19199367.

16. de Jong D, Vasmel WL, de Boer JP, et al. Anaplastic large-cell lymphoma in women with breast implants. JAMA 2008;300:2030-2035. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18984890.

17. Popplewell L, Thomas SH, Huang Q, et al. Primary anaplastic large-cell lymphoma associated with breast implants. Leuk Lymphoma 2011;52:1481-1487. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21699454.

18. Carty MJ, Pribaz JJ, Antin JH, et al. A patient death attributable to implant-related primary anaplastic large cell lymphoma of the breast. Plast Reconstr Surg 2011;128:112e-118e. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21775924.

19. U.S. Food and Drug Administration Anaplastic Large Cell Lymphoma (ALCL) In Women with Breast Implants: Preliminary FDA Findings and Analyses. 2011. Available at: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm239996.htm. Accessed November 2011.

20. Babel N, Paragi P, Chamberlain RS. Management of enteropathy-associated T-cell lymphoma: an algorithmic approach. Case Rep Oncol 2009;2:36-43. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20740143.

21. Daum S, Ullrich R, Heise W, et al. Intestinal non-Hodgkin's lymphoma: a multicenter prospective clinical study from the German Study Group on Intestinal non-Hodgkin's Lymphoma. J Clin Oncol 2003;21:2740-2746. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12860953.

22. Gale J, Simmonds PD, Mead GM, et al. Enteropathy-type intestinal T-cell lymphoma: clinical features and treatment of 31 patients in a single center. J Clin Oncol 2000;18:795-803. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10673521.

23. Wohrer S, Chott A, Drach J, et al. Chemotherapy with cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone (CHOEP) is not effective in patients with enteropathy-type intestinal T-cell lymphoma. Ann Oncol 2004;15:1680-1683. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15520071.

24. Bishton MJ, Haynes AP. Combination chemotherapy followed by autologous stem cell transplant for enteropathy-associated T cell lymphoma. Br J Haematol 2007;136:111-113. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17116129.

25. d'Amore F, Relander T, Lauritzsen GF, et al. Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. J Clin Oncol 2012;30:3093-3099. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22851556.

26. Sieniawski M, Angamuthu N, Boyd K, et al. Evaluation of enteropathy-associated T-cell lymphoma comparing standard therapies with a novel regimen including autologous stem cell transplantation. Blood 2010;115:3664-3670. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20197551.

27. Lopez-Guillermo A, Cid J, Salar A, et al. Peripheral T-cell lymphomas: initial features, natural history, and prognostic factors in a series of 174 patients diagnosed according to the R.E.A.L. Classification. Ann Oncol 1998;9:849-855. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9789607.

28. Jaffe ES. Pathobiology of Peripheral T-cell Lymphomas. Hematology 2006;2006:317-322. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17124078.

29. Dupuis J, Boye K, Martin N, et al. Expression of CXCL13 by neoplastic cells in angioimmunoblastic T-cell lymphoma (AITL): a new diagnostic marker providing evidence that AITL derives from follicular

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helper T cells. Am J Surg Pathol 2006;30:490-494. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16625095.

30. Grogg KL, Attygalle AD, Macon WR, et al. Expression of CXCL13, a chemokine highly upregulated in germinal center T-helper cells, distinguishes angioimmunoblastic T-cell lymphoma from peripheral T-cell lymphoma, unspecified. Mod Pathol 2006;19:1101-1107. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16680156.

31. Greer JP. Therapy of Peripheral T/NK Neoplasms. Hematology 2006:331-337. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17124080.

32. Horwitz SM. Management of peripheral T-cell non-Hodgkin's lymphoma. Curr Opin Oncol 2007;19:438-443. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17762567.

33. Simon A, Peoch M, Casassus P, et al. Upfront VIP-reinforced-ABVD (VIP-rABVD) is not superior to CHOP/21 in newly diagnosed peripheral T cell lymphoma. Results of the randomized phase III trial GOELAMS-LTP95. Br J Haematol 2010;151:159-166. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20738307.

34. Escalon MP, Liu NS, Yang Y, et al. Prognostic factors and treatment of patients with T-cell non-Hodgkin lymphoma: the M. D. Anderson Cancer Center experience. Cancer 2005;103:2091-2098. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15816054.

35. Schmitz N, Trumper L, Ziepert M, et al. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood 2010;116:3418-3425. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20660290.

36. Pfreundschuh M, Trumper L, Kloess M, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: results of the NHL-B1 trial of the DSHNHL. Blood 2004;104:626-633. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14982884.

37. Wilson WH, Bryant G, Bates S, et al. EPOCH chemotherapy: toxicity and efficacy in relapsed and refractory non-Hodgkin's lymphoma. J Clin Oncol 1993;11:1573-1582. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7687667.

38. Dunleavy K, Shovlin M, Pittaluga S, et al. DA-EPOCH Chemotherapy Is Highly Effective in ALK-Positive and ALK-Negative ALCL: Results of a Prospective Study of PTCL Subtypes in Adults. Blood 2011;118:Abstract 1618. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/118/21/1618.

39. Feyler S, Prince HM, Pearce R, et al. The role of high-dose therapy and stem cell rescue in the management of T-cell malignant lymphomas: a BSBMT and ABMTRR study. Bone Marrow Transplant 2007;40:443-450. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17589529.

40. Jantunen E, Wiklund T, Juvonen E, et al. Autologous stem cell transplantation in adult patients with peripheral T-cell lymphoma: a nation-wide survey. Bone Marrow Transplant 2004;33:405-410. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14676776.

41. Kim MK, Kim S, Lee SS, et al. High-dose chemotherapy and autologous stem cell transplantation for peripheral T-cell lymphoma: complete response at transplant predicts survival. Ann Hematol 2007;86:435-442. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17256144.

42. Kyriakou C, Canals C, Goldstone A, et al. High-dose therapy and autologous stem-cell transplantation in angioimmunoblastic lymphoma: complete remission at transplantation is the major determinant of Outcome-Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 2008;26:218-224. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18182664.

43. Rodriguez J, Conde E, Gutierrez A, et al. The results of consolidation with autologous stem-cell transplantation in patients with peripheral T-cell lymphoma (PTCL) in first complete remission: the Spanish Lymphoma and Autologous Transplantation Group experience. Ann Oncol 2007;18:652-657. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17229774.

44. Rodriguez J, Conde E, Gutierrez A, et al. The adjusted International Prognostic Index and beta-2-microglobulin predict the outcome after autologous stem cell transplantation in relapsing/refractory peripheral T-cell lymphoma. Haematologica 2007;92:1067-1074. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17640855.

45. Schetelig J, Fetscher S, Reichle A, et al. Long-term disease-free survival in patients with angioimmunoblastic T-cell lymphoma after high-dose chemotherapy and autologous stem cell transplantation. Haematologica 2003;88:1272-1278. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14607756.

46. Yamazaki T, Sawada U, Kura Y, et al. Treatment of high-risk peripheral T-cell lymphomas other than anaplastic large-cell lymphoma with a dose-intensified CHOP regimen followed by high-dose chemotherapy. A single institution study. Acta Haematol 2006;116:90-95. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16914902.

47. Yang DH, Kim WS, Kim SJ, et al. Prognostic factors and clinical outcomes of high-dose chemotherapy followed by autologous stem cell transplantation in patients with peripheral T cell lymphoma, unspecified: complete remission at transplantation and the prognostic index of peripheral T cell lymphoma are the major factors predictive of outcome. Biol Blood Marrow Transplant 2009;15:118-125. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19135950.

48. Blystad AK, Enblad G, Kvaloy S, et al. High-dose therapy with autologous stem cell transplantation in patients with peripheral T cell lymphomas. Bone Marrow Transplant 2001;27:711-716. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11360110.

49. Rodriguez J, Conde E, Gutierrez A, et al. Prolonged survival of patients with angioimmunoblastic T-cell lymphoma after high-dose chemotherapy and autologous stem cell transplantation: the GELTAMO experience. Eur J Haematol 2007;78:290-296. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17378891.

50. Rodriguez J, Conde E, Gutierrez A, et al. Frontline autologous stem cell transplantation in high-risk peripheral T-cell lymphoma: a prospective study from The Gel-Tamo Study Group. Eur J Haematol 2007;79:32-38. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17598836.

51. Corradini P, Tarella C, Zallio F, et al. Long-term follow-up of patients with peripheral T-cell lymphomas treated up-front with high-dose chemotherapy followed by autologous stem cell transplantation. Leukemia 2006;20:1533-1538. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16871285.

52. Mercadal S, Briones J, Xicoy B, et al. Intensive chemotherapy (high-dose CHOP/ESHAP regimen) followed by autologous stem-cell transplantation in previously untreated patients with peripheral T-cell lymphoma. Ann Oncol 2008;19:958-963. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18303032.

53. Reimer P, Rudiger T, Geissinger E, et al. Autologous stem-cell transplantation as first-line therapy in peripheral T-cell lymphomas: results of a prospective multicenter study. J Clin Oncol 2009;27:106-113. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19029417.

54. Relander T, Lauritzsen GF, Jantunen E, et al. Favorable Outcome In ALK-Negative Anaplastic Large-Cell Lymphoma Following Intensive Induction Chemotherapy and Autologous Stem Cell Transplantation (ASCT): a Prospective Study by the Nordic Lymphoma Group (NLG-T-01) [abstract]. Blood 2010;116:Abstract 3566. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/3566.

55. Sieniawski M, Lennard J, Millar C, et al. Aggressive primary chemotherapy plus autologous stem cell transplantation improves

outcome for peripheral T cell lymphomas compared with CHOP-like regimens [abstract]. Blood 2009;114:Abstract 1660. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/114/22/1660.

56. d'Amore F, Relander T, Lauritzsen GF, et al. High-Dose Chemotherapy and Autologuos Stem Cell Transplantation in Previously Untreated Peripheral T-Cell Lymphoma - Final Analysis of a Large Prospective Multicenter Study (NLG-T-01) [abstract]. Blood 2011;118:Abstract 331. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/118/21/331.

57. d'Amore F, Leppa S, da Silva MG, et al. First Interim Efficacy and Safety Analysis of an International Phase III Randomized Trial in Newly Diagnosed Systemic Peripheral T-Cell Lymphoma Treated with Chemotherapy with or without Alemtuzumab and Consolidated by High Dose Therapy [abstract]. Blood 2012;120:Abstract 57. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/120/21/57.

58. Advani R, Horwitz S, Zelenetz A, Horning SJ. Angioimmunoblastic T cell lymphoma: treatment experience with cyclosporine. Leuk Lymphoma 2007;48:521-525. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17454592.

59. Horwitz S, Moskowitz C, Kewalramani T, et al. Second-line therapy with ICE followed by high dose therapy and autologous stem cell transplantation for relapsed/refractory peripheral T-cell lymphomas: minimal benefit when analyzed by intent to treat [abstract]. Blood 2005;106:Abstract 2679. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/106/11/2679.

60. Kewalramani T, Zelenetz AD, Teruya-Feldstein J, et al. Autologous transplantation for relapsed or primary refractory peripheral T-cell lymphoma. Br J Haematol 2006;134:202-207. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16759221.

61. Rodriguez J, Caballero MD, Gutierrez A, et al. High-dose chemotherapy and autologous stem cell transplantation in peripheral T-

cell lymphoma: the GEL-TAMO experience. Ann Oncol 2003;14:1768-1775. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14630683.

62. Song KW, Mollee P, Keating A, Crump M. Autologous stem cell transplant for relapsed and refractory peripheral T-cell lymphoma: variable outcome according to pathological subtype. Br J Haematol 2003;120:978-985. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12648067.

63. Chen AI, McMillan A, Negrin RS, et al. Long-term results of autologous hematopoietic cell transplantation for peripheral T cell lymphoma: the Stanford experience. Biol Blood Marrow Transplant 2008;14:741-747. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18541192.

64. Smith S, Burns LJ, van Besien K, et al. Autologous (auto) Versus Allogeneic (allo) Hematopoietic Cell Transplantation (HCT) for T-NHL: A CIBMTR Analysis [abstract]. Blood 2010;116:Abstract 689. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/689.

65. Le Gouill S, Milpied N, Buzyn A, et al. Graft-versus-lymphoma effect for aggressive T-cell lymphomas in adults: a study by the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire. J Clin Oncol 2008;26:2264-2271. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18390969.

66. Beitinjaneh A, Saliba RM, Okoroji G-J, et al. Autologous and Allogeneic Stem Cell Transplantation for T-Cell Lymphoma: The M.D. Anderson Cancer Center Experience [abstract]. Blood 2011;118:Abstract 4118. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/118/21/4118.

67. Corradini P, Dodero A, Zallio F, et al. Graft-versus-lymphoma effect in relapsed peripheral T-cell non-Hodgkin's lymphomas after reduced-intensity conditioning followed by allogeneic transplantation of hematopoietic cells. J Clin Oncol 2004;22:2172-2176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15169805.

68. Dodero A, Spina F, Narni F, et al. Allogeneic transplantation following a reduced-intensity conditioning regimen in relapsed/refractory peripheral T-cell lymphomas: long-term remissions and response to donor lymphocyte infusions support the role of a graft-versus-lymphoma effect. Leukemia 2011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21904377.

69. Kyriakou C, Canals C, Finke J, et al. Allogeneic stem cell transplantation is able to induce long-term remissions in angioimmunoblastic T-cell lymphoma: a retrospective study from the lymphoma working party of the European group for blood and marrow transplantation. J Clin Oncol 2009;27:3951-3958. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19620487.

70. Sallah S, Wan JY, Nguyen NP. Treatment of refractory T-cell malignancies using gemcitabine. Br J Haematol 2001;113:185-187. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11328299.

71. Zinzani PL, Magagnoli M, Bendandi M, et al. Therapy with gemcitabine in pretreated peripheral T-cell lymphoma patients. Ann Oncol 1998;9:1351-1353. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9932168.

72. Zinzani PL, Venturini F, Stefoni V, et al. Gemcitabine as single agent in pretreated T-cell lymphoma patients: evaluation of the long-term outcome. Ann Oncol 2010;21:860-863. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19887465.

73. Enblad G, Hagberg H, Erlanson M, et al. A pilot study of alemtuzumab (anti-CD52 monoclonal antibody) therapy for patients with relapsed or chemotherapy-refractory peripheral T-cell lymphomas. Blood 2004;103:2920-2924. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15070664.

74. Zinzani PL, Alinari L, Tani M, et al. Preliminary observations of a phase II study of reduced-dose alemtuzumab treatment in patients with pretreated T-cell lymphoma. Haematologica 2005;90:702-703. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15921394.

75. O'Connor OA, Horwitz S, Hamlin P, et al. Phase II-I-II study of two different doses and schedules of pralatrexate, a high-affinity substrate for the reduced folate carrier, in patients with relapsed or refractory lymphoma reveals marked activity in T-cell malignancies. J Clin Oncol 2009;27:4357-4364. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19652067.

76. O'Connor OA, Pro B, Pinter-Brown L, et al. Pralatrexate in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma: Results From the Pivotal PROPEL Study. J Clin Oncol 2011;29:1182-1189. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21245435.

77. Shustov AR, Pro B, Horwitz SM, et al. Pralatrexate in patients with relapsed/refractory peripheral T-cell lymphoma (PTCL): Relationship between response and survival. ASCO Meeting Abstracts 2010;28:8054. Available at: http://meeting.ascopubs.org/cgi/content/abstract/28/15_suppl/8054.

78. O'Connor O, Pro B, Pinter-Brown L, et al. PROPEL: Results of the pivotal, multicenter, phase II study of pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) [abstract]. J Clin Oncol 2009;27:Abstract 8561. Available at: http://meeting.ascopubs.org/cgi/content/abstract/27/15S/8561.

79. Coiffier B, Pro B, Prince HM, et al. Final results from a pivotal, multicenter, international, open-label, phase 2 study of romidepsin in progressive or relapsed peripheral T-cell lymphoma (PTCL) following prior systemic therapy [abstract]. Blood 2010;116:Abstract 114. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/114.

80. Coiffier B, Pro B, Prince HM, et al. Results From a Pivotal, Open-Label, Phase II Study of Romidepsin in Relapsed or Refractory Peripheral T-Cell Lymphoma After Prior Systemic Therapy. J Clin Oncol 2012;30:631-636. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22271479.

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81. Piekarz RL, Frye R, Prince HM, et al. Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma. Blood 2011;117:5827-5834. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21355097.

82. Shustov A, Advani R, Brice P, et al. Durable remissions with SGN-35 (brentuximab vedotin): updated results of a phase 2 study in patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL) [abstract]. Ann Oncol 2011;22 (Supple 4):Abstract 125. Available at: http://annonc.oxfordjournals.org/content/22/suppl_4/iv125.full.pdf+html.

83. Shustov AR, Advani R, Brice P, et al. Complete Remissions with Brentuximab Vedotin (SGN-35) in Patients with Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma [abstract]. Blood 2010;116:Abstract 961. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/961.

84. Pro B, Advani R, Brice P, et al. Brentuximab Vedotin (SGN-35) in Patients With Relapsed or Refractory Systemic Anaplastic Large-Cell Lymphoma: Results of a Phase II Study. J Clin Oncol 2012;30:2190-2196. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22614995.

85. Damaj G, Gressin R, Bouabdallah K, et al. Results from a prospective, open-label, phase II trial of bendamustine in refractory or relapsed T-cell lymphomas: the BENTLY trial. J Clin Oncol 2013;31:104-110. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23109692.

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Mycosis Fungoides and Sézary Syndrome

Cutaneous T-cell lymphomas (CTCLs) are a group of NHLs that primarily develop in the skin, and at times progress to involve lymph nodes, blood and visceral organs. In a recent population based study of 3884 cases of cutaneous lymphomas diagnosed during 2001-2005, CTCLs accounted for 71% of cases compared with 29% for cutaneous B-cell lymphomas.[1] Based on data from the SEER program registries for the period 1998 to 2002, the annual incidence rate of CTCL was 9.6 per 1 million persons.[2] Mycosis fungoides (MF) is the most common type of CTCLs. MF accounts for about 50% to 70% of CTCL cases while Sézary syndrome (SS) accounts for only 1% to 3% of cases.[1-3] MF is an extranodal NHL of mature T-cells with primary cutaneous involvement. SS is an erythrodermic, leukemic variant of CTCL and it is characterized by significant blood involvement and lymphadenopathy. In updated EORTC and WHO classification of CTCL, MF is characterized as an indolent neoplasm.[3]

Large cell transformation (LCT) has been documented in a subgroup of patients with MF and is diagnosed when large cells are present in more than 25% of lymphoid/tumor cell infiltrates in a skin lesion biopsy.[4,5] Expert hematopathology review is needed to confirm the diagnosis, as LCT may not be easily distinguishable from other lymphoproliferative disorders. The incidence of LCT is strongly dependent on the stage of the disease at diagnosis (1.4% in early-stage disease, compared with 27% for stage IIB disease and 56%-67% for stage IV disease).[6] In published reports, the median OS from time of diagnosis of LCT ranged between 19 and 36 months.[4-7] However, in a recent study based on a large cutaneous lymphoma database, the median OS was 8.3 years and the 5-year OS rate was 63% for patients with LCT (n=70).[8] Multivariate analysis from this study showed that LCT was significantly associated with risk of disease progression but not with OS outcomes.

LCT is often, but not always, aggressive. CD30 expression of tumor cells is associated with LCT in MF or SS in 30-50% of cases.[4,6,7] This finding may have potential implications for CD30-directed therapies.

Prognosis

Published reports have identified the most significant prognostic factors for survival in patients with MF to include age at presentation, extent and type of skin involvement (T classification), overall stage, presence of extracutaneous disease and peripheral blood involvement.[8-12] Patients diagnosed with limited patch or plaque disease have an excellent prognosis, whereas those with tumor stage disease or erythrodermic skin involvement have a less favorable prognosis; patients with extracutaneous disease have a poor prognosis. Long-term follow-up data from a retrospective cohort study involving 525 patients with MF and SS showed that patient age, T classification, and presence of extracutaneous disease retained independent prognostic value in a multivariate analysis.[12] The risk of disease progression, development of extracutaneous disease or death due to MF was correlated with initial T classification. In a retrospective cohort study of 106 patients with erythrodermic MF and SS, older age, advanced disease and peripheral blood involvement were identified as adverse prognostic factors.[10] Three distinct prognostic groups (favorable, intermediate and unfavorable) were identified according to the number of unfavorable prognostic factors: 65 years or older at presentation, lymph node or visceral (stage IV) disease and peripheral blood involvement. The median survival by risk group was 10.2, 3.7, and 1.5 years, respectively.[10] In a retrospective analysis involving a large number of patients with CTCL (N=1197), the median OS in the group of patients with erythrodermic CTCL (n=124) was 5.1 years (range, 0.4–18.6 years).[13] The extent of blood involvement (as defined by flow cytometric measurements of Sézary cell counts) was significantly correlated with

survival outcomes. In multivariate analysis, advanced age and elevated lactate dehydrogenase (LDH) were the strongest predictors of poor OS.[13] In a study based on data from patients with MF/SS (N=1502) registered in a large cutaneous lymphoma database, multivariate analysis showed that advanced skin (T) stage, peripheral blood involvement, elevated LDH, and folliculotropic MF were independent factors predictive of increased risk of disease progression and decreased OS.[8] A recent study reported long-term outcomes in a large cohort of patients with MF/SS (N=1263) from a single center (seen between 1982–2009).[14] Most patients (71.5%) presented with early-stage MF (stage IA–IIA) at the time of diagnosis. Median progression-free survival (PFS) and OS was 16 years and 24 years, respectively. Approximately 12% of patients had disease progression to a higher stage, and 8% died due to the disease.[14] Significant independent factors associated with risks for progression or death included age, plaque stage, LDH levels, and tumor area.[14]

Diagnosis

In the algorithms developed by the ISCL, the diagnosis of MF is based on integration of clinical, histopathologic, immunopathologic, and molecular biological characteristics.[15] According to the revised criteria, significant blood involvement (B2) observed in SS is defined by the presence of T cells with a clonal T-cell receptor (TCR) gene rearrangement in the blood (clonally related to neoplastic T cells in the skin) and either an absolute Sézary cell count of 1000 cells/mcL or more, or increased CD4+ or CD3+ cells with CD4/CD8 ratio of 10 or higher or increased CD4+ cells with an abnormal phenotype (≥ 40% CD4+/CD7- or ≥ 30% CD4+/CD26- of total lymphocytes).

Complete skin examination, biopsy of suspicious skin sites and immunohistochemical studies of skin biopsy are essential to confirm the diagnosis. Biopsy of suspicious lymph nodes and assessment of peripheral blood for Sézary cells are recommended in the absence of a definitive skin diagnosis. MF and SS cells are characterized by the following immunophenotype: CD2+, CD3+, CD5+, CD4+, CD8-, CCR4+, CD45RO+ and they lack certain T-cell markers, CD7 and CD26.[16] There are subtypes of MF that are also CD8+, although rare. If histological evidence of large cell transformation (LCT) is observed, phenotyping with CD30 is recommended. The T-cells also express cutaneous lymphocyte antigen (CLA) and TH2 cytokines. They are also associated with a loss of TH1 and IL-12 cytokines. TCR gene rearrangement should be interpreted with caution since TCR clonal rearrangements can also be seen in non-malignant conditions or may not be demonstrated in all cases of MF/SS. Demonstration of identical clones in skin, blood and/or lymph node may be helpful in selected cases. TCR gene rearrangement analysis by PCR is a useful technique to support the diagnosis of MF/SS and to distinguish MF from inflammatory dermatoses, especially if identical clones are demonstrated in more than one skin sites.[17] A recent study evaluated the sensitivity and specificity of PCR-based TCRG and TCRB clonality tests in distinguishing MF from inflammatory dermatoses, and reported that the combined use of these tests (in sequence) was more useful than a TCRG test alone; the researchers proposed an algorithm for the sequential use of these tests in patients with intermediate pretest probabilities of having MF.[18] In at-risk populations, assessment of HTLV-1 status may be useful. HTLV-1 serology can be assessed by ELISA, and if positive, a confirmed by western blot. If the result from western blot is indeterminate, then PCR analysis for HTLV-1 can be performed.

Staging

The TNM staging system developed by the Mycosis Fungoides Cooperative Group (MFCG) had been the standard for staging and classification of patients with MF and SS.[19] Recently, the International Society for Cutaneous Lymphomas (ISCL) and EORTC recommended revisions to the MFCG staging system based on new data that emerged in the area of immunohistochemistry, biology and prognosis of MF and SS following the MFCG publication.[20,21] In the revised staging system, all staged patients should have a definitive diagnosis of MF and SS. T1 disease is defined as less than 10% of the skin surface involvement with patches or plaques and T4 disease is defined as erythroderma with at least 80% of the skin surface diffusely involved. The extent of skin involvement is based on the percentage of body surface area (BSA) where the patient's palm (without digits) is equivalent to 0.5% BSA and the palm with all 5 digits is equivalent to 1% BSA. Lymph node biopsy for staging is recommended only for clinically abnormal nodes (>1.5 cm in diameter). However, the designation "Nx" may be used for abnormal lymph nodes without histologic confirmation. Visceral disease with the involvement of an organ (e.g., spleen, liver) other than the skin, nodes or blood should be documented using imaging studies. The designation "Mx" can be used for presence of abnormal visceral sites without histologic confirmation. Blood involvement is classified into three groups: B0 is associated with the absence of significant blood involvement (5% or less of Sézary cells); B1 is defined as having a low tumor burden (more than 5% of Sézary cells but does not meet the criteria for B2); B2 is associated with high tumor burden with more than 1000 Sézary cells/mcL or increase in CD4+ cells with an abnormal phenotype (≥40% CD4+/CD7- or ≥30% CD+/CD26- of total lymphocytes). According to the updated staging system, patients with stage III are further divided into two subgroups, stages IIIA and IIIB, to differentiate based on the extent of blood involvement (B0 and B1, respectively).[20]

Workup

The initial workup of patients diagnosed with MF or SS involves a complete skin examination to assess the extent of the disease (i.e., percent of BSA), type of skin lesion (e.g., patch/plaque, tumor, erythroderma), and examination of lymph nodes or other masses for the evaluation of lymphadenopathy or organomegaly.[20] Laboratory studies should include CBC with Sézary screen (manual slide review to identify Sézary cells) and flow cytometry to assess for expanded CD4+ cells with increased CD4/CD8 ratio or with abnormal immunophenotype. A comprehensive metabolic panel and assessment of LDH levels should also be part of the initial laboratory studies. Analysis of TCR gene arrangement of peripheral blood lymphocytes is recommended if blood involvement is suspected. Patients with unfavorable features (T2 or higher, folliculotropic MF or large cell transformation, palpable adenopathy or abnormal laboratory studies) should undergo either CT or PET-CT scan of the chest, abdomen and pelvis. A CT scan of the neck may be useful in some circumstances. Integrated PET-CT was found to be more sensitive for the detection of lymph node involvement than CT alone and can help direct biopsies.[22] Bone marrow biopsy is not required for disease staging, but may be helpful in those with suspected marrow involvement (include B2 blood involvement) or in those with an unexplained hematologic abnormality.[20] Biopsy of suspicious lymph nodes (i.e., palpable nodes >1.5 cm in diameter and/or firm, irregular, clustered or fixed nodes) is recommended with evaluation for TCR gene rearrangements,[20] especially due to the worse prognosis of patients with clonal rearrangement in lymph nodes.[23]

Treatment Options for MF and SS

Initial treatment in patients with patch/plaque disease consists of skin-directed therapies (localized or generalized), with the addition of milder systemic therapy ("SYST-CAT A"; see Guidelines page MFSS-A) for refractory, persistent, or progressive disease with skin-directed therapies. Those patients who have unfavorable prognostic features (e.g., folliculotropic or large-cell transformed MF, or B1 involvement) may have systemic therapies introduced earlier in the treatment algorithm. Patients who do not respond to biologic therapy or those with very aggressive or extracutaneous disease may be treated with chemotherapy.[24-26] Due to the rarity of the condition and the need for an individualized approach, referral to a multidisciplinary academic specialty center is preferred.

Skin-directed therapies

Localized skin-directed treatments include topical therapy with corticosteroids, mechlorethamine hydrochloride, carmustine, topical retinoids (e.g., bexarotene) or topical imiquimod, or local radiation therapy (RT). Generalized skin directed therapies such as phototherapy [UVB or PUVA (psoralen and UVA)] and total skin electronic beam therapy (TSEBT) are indicated in patients with widespread skin involvement (see Guidelines page MFSS-A under "Skin-directed therapies").

Topical corticosteroids are effective, especially for the treatment of patch-stage MF, producing response rates of over 90%.[27,28] However, long-term use of topical steroid may lead to skin atrophy or striae formation and the risk becomes greater with increased potency of the steroid. Moreover, high-potency steroid used on large skin surfaces may lead to systemic absorption. Topical chemotherapy with nitrogen mustard or carmustine has been used for the management of MF for

many decades.[29,30] Long-term follow-up results from a retrospective cohort study in 203 patients with stage I-III MF have confirmed the activity and safety of topical therapy with this approach.[31] The overall response rate (ORR) was 83% (complete response [CR] in 50%). The 5-year relapse-free survival rate for patients with a CR was 42%. The median overall survival (OS) for the entire cohort was 16 years and the actuarial 10-year OS rate was 71%.[30] The efficacy with topical nitrogen mustard was similar for aqueous and ointment preparations, although the ointment was associated with reduced hypersensitivity reactions. Patients with T1 disease had higher ORR (93% vs. 72%) and CR rate (65% vs. 34%) than those with T2 disease. Moreover, patients with T1 disease had longer median OS (21 months vs. 15 months) and 5-year OS rate (97% vs. 72%) compared with patients with T2 disease.[30] A multicenter randomized phase II trial evaluated the efficacy of a topical gel formulation of the nitrogen mustard mechlorethamine compared with the compounded ointment formulation in patients with stage IA or IIA MF (N=260).[32] Eligible patients had not been treated with topical mechlorethamine within 2 years of study enrollment and had not received prior therapy with topical carmustine. Response rate based on Composite Assessment of Index Lesion Severity was 58.5% with the gel formulation compared with 48% for the ointment; these outcomes met non-inferiority criteria for the gel formulation arm. No study treatment-related serious adverse events were reported, and no systemic absorption was detected.[32]

Synthetic retinoids (bexarotene and tazarotene) and imiquimod have been used as topical therapy for the treatment of patients with MF and SS. FDA-approved bexarotene gel was evaluated in two open-label, historically-controlled clinical studies involving 117 patients with CTCL.[33,34] In the phase I-II trial involving 67 patients with early stage MF, the ORR was 63% (CR in 21%); the estimated median response

duration was 99 weeks.[33] Response rates were higher among the patients who had no prior therapy compared with those who had received prior topical therapies (75% vs. 67%). In the phase III multicenter study of 50 patients with early stage refractory MF, the ORR was 44% (CR in 8%).[34] In a small open-label pilot study in patients (N=20) with early patch or plaque MF lesions (stable or refractory to therapy), tazarotene 0.1% topical gel was reported to be a well-tolerated and active adjuvant therapy by clinical and histologic assessments.[35] In a small number of case studies, imiquimod was active in patients with early stage MF refractory to other therapies.[36-38] Bexarotene gel is the only FDA approved synthetic retinoid for topical therapy in patients with MF and SS. Given the common skin irritation toxicity observed with topical retinoids and imiquimod, these agents are best for treatment of localized, limited areas.

MF is extremely radiosensitive and patients with minimal stage IA MF may be managed effectively with local superficial RT without adjuvant therapy.[39] High disease-free survival (DFS) rates (75% at 5 years; 64% at 10 years) have been reported for patients with early stage disease treated with RT alone (N=21).[40] The 10-year DFS rate was 85% for patients with unilesional disease. The optimal RT dose was at least 20 Gy, which resulted in a DFS rate of 91% with no distant failures. In another report in patients with unilesional MF (n=18), treatment with local RT (most patients received RT dose of 30.6 Gy) resulted in an ORR of 100%, with a 10-year relapse-free survival (RFS) and OS rates of 86% and 100%, respectively.[41] TSEBT has been shown to be effective in patients with early stage MF, without the need for adjuvant therapy.[42] In patients with T1 or T2 disease (N=57) treated with TSEBT (mean total RT dose of 30 Gy), the ORR was 95%; CR was observed in 87.5% and 85% of patients with T1 and T2 disease, respectively.[42] After a median follow up of 114 months, the 5-year DFS and OS rates were

50% and 90%, respectively. The 10-year OS rate was 65%.[42] TSEBT has also been shown to be active in patients with thick generalized plaque (T2) or tumorous disease (T3). In a retrospective analysis involving 148 patients with T2 and T3 disease, TSEBT alone or in combination with adjuvant topical mechlorethamine hydrochloride yielded significantly higher CR rates compared with mechlorethamine hydrochloride alone (76% vs. 39% for T2; 44% vs. 8% for T3).[43] The standard dose of TSEBT is 30-36 Gy (given in fractions over 8 to 10 weeks), but recent studies suggest that lower radiation doses may be sufficiently active. A recent retrospective study in patients with T2 to T4 disease (N=102; excluded patients with extracutaneous disease) treated with TSEBT doses of 5 to <30 Gy showed ORR (>50% improvement) of 96% and CR rate of 31%.[44] The ORR among the subgroup that received 5 to <10 Gy (n=19), 10 to <20 Gy (n=52), and 20 to <30 Gy (n=32), were 90%, 98% and 97%, respectively. The CR rate with TSEBT 5 to <30 Gy was higher among patients with T2 compared with T3 disease (41% vs. 17%).[44] In patients with T2 or T3 disease, OS and PFS outcomes were not significantly different by dose groups and were comparable to that of standard dose TSEBT (i.e., ≥30 Gy).[44] The lower dose ranges with TSEBT 10 to <20 Gy warrants further evaluation, especially in combination regimens. In a recent prospective study, patients with stage IB-IV MF (N=10) were treated with TSEBT 1 Gy weekly (for a total dose of 10 Gy).[45] The ORR was 90% and 70% achieved a CR or very good partial remission (PR)(<1% skin affected by patches/plaques). The median duration of response was 5 months. Low dose of TSEBT was well tolerated in this patient population; further studies of its use in combined modality regimens are warranted.

Phototherapy with UVB (including narrowband) and photochemotherapy with psoralen and UVA (PUVA) are effective alternative treatment

options for patients with early stage MF.[46-49] In a retrospective analysis of patients with stage IA or IB (N=56), phototherapy with narrowband UVB (n=21) and PUVA (n=35) produced similar CR rates (81% vs. 71%) and mean relapse-free interval (24.5 months vs. 23 months).[46] In another retrospective study in a larger group of patients with early-stage MF (stages IA–IIA; N=114), treatment with narrowband UVB (n=19) and PUVA (n=95) also resulted in similar CR rates (68% vs. 62%) and median time to relapse (11.5 months vs.14 months).[48] In a retrospective analysis of long-term follow-up data from patients with early-stage MF (stages IA–IIA) who achieved a CR with PUVA (N=66), 10-year DFS rates were 30% for patients with stage IA disease and 50% for those with stage IB/IIA disease.[47] The median follow-up time was 94 months. The 10-year OS rates were 82% and 69%, respectively; interestingly, OS outcomes were not different by relapse status. A third of patients developed signs of chronic photodamage and secondary cutaneous malignancies.[47] It should be noted that cumulative doses of UV are associated with increased risk of UV-associated skin malignancies. Thus, phototherapy may not be appropriate for patients with a history of squamous or basal cell carcinoma or melanoma. Since narrowband UVB has less skin toxicity than broadband and PUVA, it is preferred to start with narrowband UVB than PUVA in early-stage patients with patch or thin plaque disease.

Systemic therapies

There are extensive data—although primarily from small clinical studies—on many systemic therapeutic options for CTCL. Historically, the response criteria for CTCL were poorly defined and validated response assessments were lacking. More recent studies have incorporated consensus response assessments and newer FDA-approved agents have undergone central review for efficacy outcomes.

Systemic therapies with extracorporeal photopheresis (ECP), interferons, systemic retinoids, or histone deacetylase (HDAC) inhibitors are preferred over traditional chemotherapy for patients who do not respond to initial skin-directed therapies (see Guidelines page MFSS-A under "SYST-CAT A"). Multiagent chemotherapy is generally reserved only for patients who do not respond to multiple prior therapies (including single-agent chemotherapy and combination regimens) or those with bulky lymph node or solid organ disease. In the absence of other unfavorable prognostic features, it is recommended that systemic therapy be deferred until the patient has failed multiple treatments with local and skin-directed therapy.

ECP is an immunomodulatory therapy using psoralen and UVA extracorporeally. This approach involves the removal of leukocytes by leukapheresis, which are then treated with 8-methoxypsoralen, exposed to UVA and returned to the patient. ECP is a long standing treatment for MF, and is particularly indicated in patients with or at risk of blood involvement (erythrodermic stage III disease or IVA with SS).[50-52] In small retrospective studies with ECP (generally given for at least 6 months) in patients with CTCL, ORR ranged from about 50-70% with a CR in 15-25%; median OS was 6-8 years, and 5-year OS rate was reported to be 80% in one study.[52-54] In a meta-analysis of 19 studies (5 studies using ECP as monotherapy and 14 studies as combination therapy) involving more than 400 patients with CTCL, the combined ORR for all stages of CTCL was 56% with 18% achieving a CR.[51] ECP as monotherapy resulted in 55.5% ORR with 15% CR.[51] The corresponding response rates were 58% (15% CR) for erythrodermic disease (T4) and 43% (9.5% CR) for SS. Studies evaluating combination regimens with ECP are discussed below, in the section "Combination Therapies".

Retinoids [all-trans retinoic acid (ATRA),13-cis retinoic acid and their synthetic analogs acitretin and isotretinoin] and interferons have been used for many years for the treatment of CTCL.[55,56] Interferon (IFN) alpha as a single agent has produced ORR greater than 70% with CR rates greater than 20%.[55] IFN gamma has been shown to be effective in the treatment of patients with various stages of CTCL that is refractory to IFN alpha and other topical or systemic therapies.[57]

Oral bexarotene has been evaluated for the treatment of refractory or persistent early- and advanced-stage CTCL in two multicenter clinical trials.[58,59] In patients with early-stage CTCL (stages IA-IIA) refractory to prior treatment, bexarotene was well tolerated and induced an ORR of 54% among patients treated at doses of 300 mg/m^2/day (n=28).[59] The rate of disease progression at this dose was 21%, and the median duration of response had not been reached at the time of the report. In patients with advanced CTCL (stages IIB–IVB) refractory to prior treatments, clinical CR and PR were observed in 45% of patients receiving 300 mg/m^2/day (n=56). At doses greater than 300 mg/m^2/day (n=38), the ORR was 55%, including 13% clinical CR.[58] Side effects were reversible and manageable with appropriate medications prior to initiation of treatment. In a retrospective comparison study, ATRA and bexarotene were reported to induce similar outcomes with modest single-agent activity in the treatment of patients with relapsed MF and SS.[60] Bexarotene (oral capsules) is approved by the FDA for the treatment of refractory CTCL.

HDAC inhibitors are a new class of drugs that are potent inducers of histone acetylation, cell cycle arrest and apoptosis. The activity and safety of the HDAC inhibitors vorinostat and romidepsin were evaluated in patients with refractory CTCL in phase II trials.[61-64] In a phase IIb study involving 74 patients (median 3 prior therapies) with persistent, progressive or refractory stage IB to IVA MF/SS, vorinostat resulted in

an ORR of 30% and median time to progression of 5 months.[62] Median time to progression was greater than 9.8 months in responders with advanced disease (stage IIB or higher).[62] The response rates and median response durations appeared to be comparable to those obtained with bexarotene capsules and denileukin diftitox. Vorinostat was the first HDAC inhibitor to receive FDA approval for the treatment of patients with progressive, persistent, or recurrent CTCL, on or following two systemic therapies. A *post-hoc* subset analysis of patients who experienced clinical benefit with vorinostat in the previous phase IIb study and received 2 or more years of vorinostat therapy (n=6) provided some evidence for the long-term safety and clinical benefit of vorinostat in heavily pretreated patients, regardless of previous treatment failures.[65]

Romidepsin demonstrated single-agent activity in 2 open-label clinical studies [pivotal phase 2B study (GPI-04–0001) and NCI 1312 (supportive study)] of 167 patients with CTCL refractory to prior therapies.[64,66] The pivotal phase IIb study (GPI-04-0001) enrolled 96 patients with stage IB to IVA CTCL (71% had advanced stage disease ≥ stage IIB; median 2 prior systemic therapies).[64] The ORR was 34% (CR in 6%). Among patients with advanced stages of disease, 38% achieved an objective response (CR in 7%).[64,67] The median time to response was 2 months and the median duration of response was 15 months. Improvement in pruritus was observed in 28 of 65 patients (43%) with moderate to severe symptoms at baseline, including in 11 patients who did not achieve an objective response.[67] These results are consistent with the findings of the phase NCI 1312 (supportive study) in a similar population (N=71) using the same dose and schedule of romidepsin, where the ORR was 34% (CR in 7%) and the median duration of response was 14 months.[68] In the pivotal study, romidepsin also induced clinically significant responses in patients with blood

involvement.[69] Among evaluable patients (n=27), the ORR was 32% by composite assessment, including 2 clinical CRs. In a pooled analyses of these two international multicenter clinical studies, objective response was seen 41% of patients (CR in 7%) in the evaluable population (patients who had at least 2 cycles of romidepsin; n=135).[63] Responses were noted in 42% of patients with stage IIB or greater MF and 58% of patients with SS. Median duration of response and median time to disease progression were 15 months and 8 months, respectively.[63] Romidepsin is approved by the FDA for the treatment of CTCL in patients who have received at least one prior systemic therapy.

Denileukin diftitox is a recombinant fusion protein with interleukin-2 (IL-2) and diphtheria toxin, and targets the high-affinity IL-2 receptor (CD25) expressed on malignant T-cells and B-cells. Although denileukin diftitox was FDA approved for the treatment of patients with persistent or recurrent CTCL based on phase III studies,[70,71] the agent is currently not available (as of June 2012); the manufacturer recently terminated a phase III study in PTCL to prioritize the development of a new improved formulation of the drug.

Conventional cytotoxic systemic chemotherapy is used as a primary treatment only for patients with advanced disease, i.e., stages IIB-IV (see Guidelines page MFSS-A for treatments under "SYST-CAT-B" and "SYST-CAT-C") or large cell transformation (see pages MFSS-6 and MFSS-A for treatments under "SYST-CAT-C") and for second-line therapy for early-stage disease refractory to skin-directed therapies and systemic biologic therapies (see page MFSS-5 for refractory disease). Low-dose methotrexate has been used to treat early-stage MF and SS for many years, although only limited data are available.[72,73] Gemcitabine as a single agent has been evaluated in patients with advanced, heavily pretreated CTCL and as front-line therapy in untreated patients.[74-77] Another nucleoside analog pentostatin has

shown activity either as a single agent or in combination with IFN alpha in patients with advanced MF or SS.[78-80] Limited data also suggest some activity for the oral alkylating agent temozolomide and the proteasome inhibitor bortezomib in patients with previously treated MF.[81,82]

Pegylated liposomal doxorubicin has shown substantial single-agent activity in patients with pretreated, advanced or refractory CTCL.[83-85] In a small prospective phase II trial in patients with previously treated CTCL (N=19; MF, n=13 [including transformed MF in n=3]; SS, n=3), pegylated liposomal doxorubicin induced an ORR of 84% (CR in 42%) with no significant differences between patients with stage I-IIA and IIB-IV disease.[84] After a median follow up of 23 months, the median event-free survival and OS was 18 months and 34 months, respectively. In another prospective study in patients with advanced or refractory MF/SS (N=25), the ORR was 56% (CR in 20%) with pegylated liposomal doxorubicin.[85] The median OS was 44 months. A phase II multicenter trial from the EORTC evaluated pegylated liposomal doxorubicin in patients with advanced MF (stage IIB, IVA, IVB) refractory or relapsed after at least 2 prior systemic therapies.(N=49).[86] The ORR was 41% (CR in 6%). The median time to progression was 7 months and the median duration of response was 6 months. Single-agent therapy with pegylated liposomal doxorubicin was well tolerated with no grade 3 or 4 hematologic toxicities; the most common grade 3 or 4 toxicities included dermatologic toxicity other than hand and foot reaction (6%), constitutional symptoms (4%), gastrointestinal toxicities (4%) and infection (4%).[86] A recent phase II study evaluated pegylated liposomal doxorubicin followed sequentially by oral bexarotene in patients with advanced-stage or refractory CTCL (N=37; stage IV, n=21 [including SS, n=7]; stage IIB, n=10; refractory, n=6).[87] Treatment with 8 doses (16 weeks) of liposomal doxorubicin resulted in an ORR of 41%

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including clinical CR in 2 patients (n=34 evaluable). The maximum response was observed after 16 weeks of treatment with liposomal doxorubicin; sequential bexarotene did not improve the response rate or duration. At the time of follow up (median 7.5 months for surviving patients), the median PFS was about 5 months.[87]

Pralatrexate is a folate analog indicated for patients with relapsed/refractory peripheral T-cell lymphoma (PTCL), and has also demonstrated activity in patients with CTCL. In a multicenter dose-finding study, pralatrexate 10 mg/m^2 to 30 mg/m^2 (given weekly for 2 of 3 weeks or 3 of 4 weeks) was evaluated in patients with relapsed or refractory CTCL (N=54; MF, n=38 [70%]; SS, n=15 [28%]).[88] Patients had received a median of 4 prior systemic therapies (range, 1–11). The recommended dose was identified as 15 mg/m^2 weekly for 3 weeks of a 4-week cycle. The ORR for all evaluable patients on this study was 41% (CR in 5.5%). Among the patients (in the dose-finding cohort and expansion cohort) who received the recommended dose (as above; n=29), the ORR was 45% (CR in 3%).[88] Thus, low-dose pralatrexate was shown to have high activity in patients with heavily pretreated CTCL.

Based on limited data from clinical studies and case report, liposomal doxorubicin, denileukin diftitox and gemcitabine have shown some activity in patients with transformed MF.[85,89,90] In the subgroup of patients with relapsed/refractory transformed MF (n=12) treated on the PROPEL trial that evaluated pralatrexate (30 mg/m^2 weekly for 6 weeks of a 7-week cycle) in patients with PTCL, the ORR based on investigator assessment and by independent review was 58% and 25%, respectively.[91,92] Based on investigator assessment, the median duration of response was 4 months and median PFS was 5 months. The median OS was 13 months.[91]

Combination therapies

Combinations of biologic or non-cytotoxic therapies as distinct from combination chemotherapies are used when single-agent therapies fail or in cases of advanced, progressive, or refractory disease (see Guidelines page MFSS-A for regimens under "Combination Therapies"). The rationale for such systemic combination strategies in CTCL is to provide synergistic efficacy without additive toxicities. Combinations of systemic agents with skin-directed therapies are often used to maximize clinical responses in the skin compartment. Several combination therapies have been studied in clinical trials for CTCL. Most commonly used combination regimens include phototherapy plus either IFN or systemic retinoid, and ECP plus either IFN or systemic retinoid or both.[93-99] PUVA when used in combination with IFN alfa produced an ORR of 93% (CR in 80%) in patients with stage IB to stage IVB disease evaluated in a phase I trial (N=15); the median duration of response exceeded 23 months.[93] In a prospective randomized study evaluated IFN combined with PUVA versus IFN combined with retinoids in patients with stage I or II CTCL (N=82 evaluable), the combination of IFN with PUVA resulted in significantly higher CR rates in this patient population (70% vs. 38%).[97] In a phase II trial in patients with symptomatic MF/SS (N=63; stages IA-IIA, n=43; stages IIA-IIB, n=6; and stages III-IVA, n=14). IFN combined with PUVA (followed by PUVA maintenance in patients with a CR) resulted in a CR in 75% of patients, with a median duration of response of 32 months.[99] The 5-year DFS and OS rates were 75% and 91%, respectively. In another prospective phase II trial in patients with early-stage MF (stages IA-IIA; N=89), the combination of low-dose IFN alfa with PUVA resulted in an ORR of 98% (CR in 84%).[94] Low-dose bexarotene in combination with PUVA also resulted in high response rates with an ORR of 93% (CR in 47%) in a small group of patients with MF/SS (all stages) resistant or intolerant to previous therapies (N=15).[100] However, a phase III randomized study

from the EORTC recently reported no significant differences in outcomes using the combination of bexarotene with PUVA compared with PUVA alone in patients with early stage MF (stage IB and IIA; N=93).[101] The ORR with the combination was 77% (CR in 31%) compared with 71% (CR in 22%) with PUVA alone; the median duration of response was 5.8 months and 9,7 months, respectively. A trend towards fewer PUVA sessions and lower UVA doses to achieve CR was observed with the combination arm, although the differences were not significant.[101] This trial was closed prematurely due to low patient accrual.

The combination of biologic agents with ECP has been shown to improve response rates in patients with advanced stage CTCL.[53,98,102] In a retrospective study involving patients with advanced CTCL (N=47), ECP with or without biologic agents (i.e., IFN, systemic retinoids, sargramostim) resulted in an ORR of 79% (CR in 26%) with a median OS of 74 months.[98] The median OS in the subgroup of patients with stage III or IV disease with blood involvement was 55 months. The combined modality therapy (ECP with IFN and/or systemic retinoids) resulted in improved response rates (84% vs. 75%) and median OS (74 months vs. 66 months) compared with ECP alone despite poor prognostic features among patients treated with combined modality therapy; these differences in outcomes were not statistically significant, however.[98] In a recent retrospective cohort study of patients with SS (N=98) who received at least 3 months of ECP combined with 1 or more biologic agents (i.e., IFN alfa, systemic retinoid, IFN gamma, and/or GM-CSF), the ORR was 75% with CR in 30% of patients.[102] Most patients on this study received ECP in combination with IFN alfa (89%) and/or systemic retinoids (86%); 30% of the patients were treated with ECP combined with both IFN alfa and systemic retinoids. The 5-year OS rate from time of diagnosis was 55% and the median OS was

65%.[102] The 5-year OS rates for the subgroups of patients with stage IIIB, IVA1, IVA2, and IVB were 80%, 80%, 76%, and 0%, respectively. A higher monocyte percentage at baseline was significantly associated with CR rates.[102]

Systemic retinoids have been studied in combination with other biological response modifiers in patients with advanced disease. The combination of low-dose bexarotene and low-dose IFN alfa was reported to have synergistic activity in a small case series of patients with CTCL (erythrodermic CTCL and follicular MF).[103] In a phase II study in patients with CTCL (N=22; all stages) oral bexarotene (at standard doses; 300 mg/m^2/day for at least 8 weeks) was evaluated in combination with IFN alfa (added in cases of <CR after 8 weeks of bexarotene alone).[104] Among evaluable patients (n=18), the ORR for the combined regimen was 39% (CR in 6%). Although the regimen was well tolerated, response rates were not improved relative to the ORR expected with bexarotene alone.[58,59] The combination of bexarotene and denileukin diftitox is particularly interesting given that bexarotene has been shown to increase CD25 expression in CTCL cells, thereby potentially increasing the susceptibility of T-cells to denileukin diftitox. In a phase I study in patients with relapsed/refractory CTCL (N=14), denileukin diftitox combined with bexarotene resulted in an ORR of 67% (CR in 28.5%).[105] Lastly, combined modality therapy with oral isotretinoin and IFN alfa (followed by TSEBT and maintenance therapy with topical nitrogen mustard and IFN alfa) was evaluated in patients with MF (N=95; stages IA-IIA, n=50; stages IIB-IVB, n=45) in a long-term follow-up study.[106] The ORR was 85% with CR in 60% of patients; the CR rate was 76% among patients with early-stage MF (remission >5 years in 24% of responders) and 40% among those with advanced stage disease (remission duration >5 years in 17%). The median DFS and OS rate for patients with early-stage disease was 62 months and

145 months, respectively. The corresponding endpoints for patients with advanced stage disease were 7 months and 36 months, respectively. The 5-year estimated OS rate was 94% for patients with early-stage and 35% for advanced-stage MF. Disease stage was the only independent prognostic factor for survival based on multivariate analysis.[106]

NCCN Recommendations Based on Clinical Stage

Primary Treatment

The NCCN Guidelines panel recommends that patients diagnosed with MF/SS be treated at specialized centers with expertise in the management of this disease. It should be noted that unlike other NHL subtypes, response criteria for MF/SS has not been shown to correlate with prognosis. The decisions to continue with or switch treatment regimens are often made based on clinical parameters. A proposal for detailed response criteria for MF/SS, according to consensus from an international group of experts, was recently published.[21]

Patients with stage IA disease have an excellent prognosis using skin-directed therapies alone, where their life expectancy is not altered compared with matched control populations.[8,12] Stage IA is managed primarily with skin-directed therapies, alone or in combination with other skin-directed therapies including local RT (see page MFSS-4). Local RT (12–36 Gy) is recommended particularly for unilesional presentation. Treatment options include topical corticosteroids, topical chemotherapy (i.e., nitrogen mustard or carmustine), topical retinoids (i.e., bexarotene or tazarotene), topical imiquimod, and/or phototherapy (UVB for patch or thin plaques; PUVA for thicker plaques) (see page MFSS-A). Patients with a PR to initial therapies (i.e., having persistent T1 skin disease) should be treated with other options from the list of recommendations therapies mentioned above.

Patients with stage IB-IIA disease require generalized skin treatment (see page MFSS-5). Topical retinoids are not recommended for generalized skin involvement because these treatments can cause substantial irritation. In addition to the other skin-directed therapies used for stage IA disease (as mentioned above), TSEBT (12–36 Gy) is another treatment option for those with severe skin symptoms or generalized thick plaque or tumor disease (see page MFSS-A. Although TSEBT is highly effective in T1 disease (stage IA), it is reserved for generalized or recalcitrant skin disease due to its toxicities and lack of superior long-term outcome. It is common practice to follow TSEBT with systemic therapies such as interferon or bexarotene to maintain response. For patients with sites that are not responsive to generalized treatment, additional treatment may be needed. Patients with persistent T1 skin disease should be treated with skin-directed therapies as mentioned for patients with stage 1A disease; patients with persistent T2 disease should be treated with other options from the list of treatments for generalized skin involvement, as mentioned above.

Patients with early stage disease (stage IA, stage IB-IIA) with B1 blood involvement are often best managed with more intensive treatments as described for stage III with B1 blood involvement (see Discussion below). Patients with histological evidence of folliculotropic or large cell transformation (LCT) are usually managed as described for treatment of stage IIB disease (see Discussion below).

Patients with stage IIB disease and/or histological evidence of folliculotropic or LCT can be separated into two categories: 1) limited extent tumor disease with or without patch/plaque disease; or 2) generalized tumor disease, transformed and/or folliculotropic disease (see page MFSS-6). In patients with tumor disease, rebiopsy is necessary if LCT is suspected. Patients with limited extent tumor disease can be managed with local RT for tumor lesions. Combination

or adjuvant systemic therapy (SYST-CAT A: retinoids, IFNs, HDAC inhibitors, ECP, methotrexate [≤100 mg per week]) may be considered to improve overall response and duration of response. Skin-directed therapies, as described above for stage I-IIA disease, can be used for residual patch or plaque lesions.

Patients with generalized tumor disease are treated with TSEBT or systemic therapy, with or without skin-directed therapy. For patients treated with TSEBT, adjuvant therapy with systemic therapies (SYST-CAT A) can be considered to improve response duration. For systemic therapy, recommended options include treatments listed under SYST-CAT A (as listed above), SYST-CAT B (first-line: liposomal doxorubicin, gemcitabine; second-line: chlorambucil, pentostatin, etoposide, cyclophosphamide, temozolomide, methotrexate [>100 mg per week], bortezomib, low-dose pralatrexate), or SYST-CAT C (liposomal doxorubicin, gemcitabine, romidepsin, low-dose or standard-dose pralatrexate, regimens recommended for PTCL in the NHL Guidelines), or combination therapies.

Systemic therapy is the initial treatment for patients with LCT (see pages MFSS-6 and MFSS-A). If there is no evidence of aggressive growth, systemic therapies from SYST-CAT A or SYST-CAT B are appropriate. Patients with indolent/plaque folliculotropic MF (without evidence of LCT) should initially be considered for options under SYST-CAT A before resorting to treatment options listed under SYST-CAT B or SYST-CAT C. For LCT with aggressive growth, the NHL Guidelines panel recommends systemic therapy with options listed under SYST-CAT C). Combination regimens are generally reserved for patients with relapsed or refractory or extracutaneous disease. Following completion of primary therapy, patients with persistent T1 or T2 disease should be treated with skin-directed therapies for limited (T1) or generalized (T2) skin involvement. Patients with persistent T3

limited extent disease should continue to receive local RT with adjuvant systemic therapy (SYST-CAT A), or systemic therapy (with or without skin-directed therapies and with or without RT). Patients with persistent T3 disease should continue to receive TSEBT, systemic therapies, or combination therapies, with or without skin-directed therapies.

Management of patients with stage III disease depends on the extent of blood involvement (see page MFSS-7): no significant blood involvement (B0) or some blood involvement (B1), which is less than that observed for SS (B2). Patients with no significant blood involvement are treated with generalized skin-directed therapies similar to those recommended for stage IB -IIA (see page MFSS-A). Generalized skin-directed therapies should be used with caution in patients with stage III disease, as treatments other than topical steroids may not be well tolerated. Phototherapy (PUVA or UVB) or TSEBT may be used successfully in these patients. ECP may be a more appropriate systemic therapy for patients with stage III disease with blood involvement. Alternative options include other treatment options listed under SYST-CAT A, with or without skin-directed therapy. Mid-potency steroids should be used in combination with systemic therapy to reduce skin symptoms. Antibiotic therapy should be considered for this group of patients since they are at increased risk of developing secondary infections. Patients with inadequate response or persistent disease should be treated with other options within the list of primary treatments (generalized skin-directed treatments or for blood involvement, SYST-CAT A with or without skin-directed therapy).

Stage IV disease includes SS and non-Sézary or visceral (solid organ) disease. SS patients are treated with single agent systemic therapy (agents listed in SYST-CAT A) or combination therapies (see pages MFSS-8 and MFSS-A). Safety data on the use of systemic retinoids in combination with TSEBT and vorinostat in combination with

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phototherapy or TSEBT is currently lacking. Non-Sézary or solid organ disease is frequently managed with systemic therapy (SYST-CAT B or SYST-CATC) with or without RT for local control. These patients may present with more aggressive growth characteristics. If there is no evidence of aggressive growth, systemic therapies from SYST-CAT B would be more appropriate. In cases where aggressive growth is observed, the regimens listed under SYST-CAT C would be preferred. Adjuvant biologic therapy may be considered following chemotherapy to improve response duration.

All patients (stage IA through stage IV) showing response (and/or clinical benefit) should be considered for maintenance or tapering therapy to optimize response duration. Patients with a PR or disease relapse following primary treatment should be treated with the other options included in the primary treatment to improve response before starting treatment for refractory disease. In addition, patients with disease relapse or persistent disease may be considered for clinical trials. Patients with stage IV disease should be considered for clinical trials.

Refractory, Progressive, or High-Risk/Advanced Disease

Role of Allogeneic Stem Cell Transplantation
Autologous stem cell transplantation (SCT) has been used infrequently for patients with CTCL. In general, the duration of response have been short, thus limiting its utility and uptake.[107] Allogeneic SCT has been reported only in case reports or small series in patients with advanced MF and SS,[107-111] or in retrospective studies.[112-114] Several of these published cases reported on the association between graft-versus-host-disease and tumor response, or the reinduction of remission following withdrawal (or reduction) of immunosuppression, suggesting that graft-versus-tumor effect may play an important role in the extent of disease

control achieved with allogeneic SCT.[108,109,111-113] A meta-analysis compared the outcome of allogeneic versus autologous SCT in patients with MF and SS based on patient cases derived from the literature (N=35).[115] The analysis suggested that OS outcomes and response durations were more favorable among the patients who received allogeneic SCT.[115] In the allogeneic SCT group, the majority (70%) of patients experienced persistent graft-versus-host disease (GVHD), which was primarily mild to moderate in severity. Whereas the majority of the deaths among patients undergoing autologous SCT may be attributable to progressive disease,[115] deaths associated with allogeneic SCT may be more due to non-relapse mortality (NRM). The incidence of NRM in published reports with allogeneic SCT is about 21% to 25%.[112-114] In a study that evaluated TSEBT with allogeneic HSCT in patients with advanced CTCL (N=19), the ORR was 68% (CR in 58%) with median OS not reached at the time of the report; the TRM rate was 21%.[113] In a retrospective analysis of patients with MF/SS registered in the EBMT database (N=60), the 3-year PFS and OS rate with allogeneic SCT was 34% and 54%, respectively.[112] The NRM rate at 2 years was 22%. Outcomes were not significantly different between histology types. However, patients with advanced-stage disease had a higher 3-year relapse rate compared with those with earlier stage disease (53% vs. 25%; *P*=0.02). The use of reduced-intensity conditioning was associated with significantly lower 2-year NRM rate (14% vs. 49%; *P*=0.021) and higher 3-year OS rate (63% vs. 29%; *P*=0.019) compared with myeloablative conditioning; the relapse rate at 2 years was not different between these subgroups. In addition, transplantation from matched related donors was also associated with significantly lower NRM rate (16% vs. 40%; *P*=0.035) and higher OS rate (63% vs. 24%; *P*=0.001) compared with transplantation from unrelated donors.[112] Allogeneic SCT appears to be a promising therapeutic strategy in patients with advanced CTCL. Further data from

prospective studies are needed to establish the role of allogeneic SCT in these patients.

Alemtuzumab
Alemtuzumab, a humanized anti-CD52 monoclonal antibody, has shown promising activity in patients with advanced MF and SS.[116-121] In studies using standard dose alemtuzumab (IV or SC; 30 mg thrice weekly for up to 12 weeks) in heavily pretreated patients with advanced MF or SS, the ORR was 38% to 84% (CR in 0–47%); most patients progressed within 4 to 6 months.[116,121,122] In a phase II study in patients with advanced MF/SS (N=22; stage III-IV in 86%; median 3 prior therapies), the ORR with single-agent alemtuzumab was 55% (CR in 32%).[116] The median time to treatment failure (in responding patients) was 12 months. In a recent study of alemtuzumab in heavily pretreated patients with relapsed/refractory erythrodermic MF and SS (N=19), the ORR was 84% (CR in 47%); median PFS and OS was 6 months and 41 months, respectively.[122] Major toxicities with alemtuzumab included myelotoxicities and infectious complications (including those attributed to cytomegalovirus reactivation), thus prompting the investigation of lower doses of alemtuzumab.[118,119] In a study of patients with SS (N=14; relapsed/refractory SS, n=11), SC alemtuzumab at low doses (3-15 mg per administration) given for a short time period based on Sézary cell count, was associated with an ORR of 86% (CR in 21%) with an acceptable toxicity profile.[118] The median time to treatment failure was 12 months. None of the patients who received the 10 mg dose developed hematologic toxicities or infections, which suggested that low-dose alemtuzumab (up to 10 mg per dose) may be a reasonable regimen for patients with pretreated SS.

Management of Relapsed, Progressive Stage IA-IIB Disease
Clinical trial participation or systemic therapy with agents listed under SYST-CAT A, as single agent or combination therapy, is recommended for patients with stage IA, IB-IIA disease that is progressive or refractory to primary skin-directed therapies (see page MFSS-5). Skin-directed therapy can be used as adjuvant treatment to reduce skin symptoms. Patients who do not respond to treatment with agents under SYST-CAT A should be considered for clinical trial, TSEBT (if not previously administered) or in the absence of a suitable clinical trial, treated with single agent systemic chemotherapy with regimens listed under SYST-CAT B.

In patients with refractory or progressive stage IIB disease with limited-extent tumor disease (with or without patch/plaque), options may include those used as primary treatment for stage IIB generalized extent tumor disease (see page MFSS-6); these options include TSEBT (with or without adjuvant systemic therapy from SYST-CAT-A to improve response duration), systemic chemotherapy, or combination therapies—with or without skin-directed therapies. In patients with stage IIB disease refractory to or progressive with these treatment options, options may include multiagent chemotherapy, consideration for allogeneic SCT or clinical trial participation. Patients are generally treated with multiple agents from SYST-CAT A or SYST-CAT B or with combination therapies before receiving multiagent chemotherapy.

Management of Relapsed Stage III or High-Risk Disease
In patients with refractory or progressive stage III disease, combination therapy or clinical trial should be considered (see page MFSS-7); if the patient remains refractory or progresses during second-line therapy, then clinical trials, systemic therapy with agents listed under SYST-CAT B, or allogeneic SCT (including options using non-ablative conditioning) may be considered. Alemtuzumab may also be considered in this setting. For patients with stage IV/SS or non-Sézary disease with relapse (following a response) or persistent disease (inadequate response), allogeneic SCT may be considered, as appropriate. For

patients with refractory or progressive SS (non-response to primary treatment), systemic therapy with agents listed under SYST-CAT B, alemtuzumab, or clinical trial participation would be appropriate options. For patients with refractory or progressive non-Sézary or visceral disease, clinical trials should be considered.

Considerations for Allogeneic SCT

As mentioned above, allogeneic SCT may be considered for patients with stage IIB-IV disease that is progressive or refractory to primary treatment options. Appropriate patients (stage IIB or stage III MF who have failed multiple systemic therapies/combination therapies and adequate trial of skin-directed therapy; high-risk stage IV patients with relapse or inadequate response following primary treatment with systemic therapies, combination therapies and/or multiagent chemotherapy) may be referred for a transplant consultation. In general, patients should have failed biologic options and single agent chemotherapy prior to allogeneic SCT. When appropriate, TSEBT may be considered as cytoreductive therapy before transplant. Patients with relapsed/progressive disease only in the skin should not be referred for transplant. The ideal timing for allogeneic SCT is when the disease is well controlled with induction therapy and before the disease has progressed to a state where the chance of response or survival with allogeneic SCT is low. This is particularly true for patients with high-risk stage IV disease that has relapsed (or has persistent disease) after primary treatment. For these patients, consideration of allogeneic SCT should be made earlier in the treatment phase to optimize response to induction therapy prior to transplant. Thus, for high-risk stage IV disease, allogeneic SCT should not be a 'last resort' option.

Currently there is no definitive treatment for advanced disease that can produce reliable durable remissions or curative results, other than

possibly, allogeneic SCT. The NCCN Guidelines recommend participation in a clinical trial as a treatment option for all patients with relapsed or progressive disease.

Supportive Care for Patients with MF/SS

Management of Pruritus

Symptoms of pruritus can be present in a large majority (nearly 90%) of patients with CTCL, and may be associated with decreased quality of life for patients.[123,124] Patients with MF/SS should be evaluated for pruritus at each visit. Other potential causes of pruritus (e.g., contact dermatitis, atopic dermatitis, psoriasis, other inflammatory skin conditions) should be ruled out. The extent of pruritus should be determined (localized vs. generalized), and potential correlation between disease site and localization of pruritus should be noted. Daily use of moisturizers and emollients are helpful in maintaining and protecting the skin barrier. The treatment of pruritus requires optimizing skin-directed and systemic treatments. Topical steroids (with or without occlusion) can be effective in managing the disease and accompanying pruritus in early-stage disease. [125,126] First-line options with systemic therapies include antihistamines, the tricyclic antidepressant doxepin or the anticonvulsant gabapentin.[125,127] In the second-line setting, systemic therapy with the neurokinin-1 receptor antagonist aprepitant, the tetracyclic antidepressant mirtazapine or use of selective serotonin reuptake inhibitors may be considered.[125,127-129] Treatment with the oral opioid receptor antagonist naltrexone may be considered if symptoms of pruritus do not resolve with the above agents.[130-132]

Prevention and Treatment of Infections

Infectious complications are frequent among patients with MF/SS, particularly cutaneous bacterial infections and cutaneous herpes viral infections (e.g., HSV or HZV infections).[133] Bacteremia/sepsis and

bacterial pneumonia were reported as the major cause of death due to infections in a retrospective cohort study of patients with MF/SS.[133] Several preventive measures can be incorporated to minimize infectious complications in patients with MF/SS. These measures include maintaining/protecting the skin barrier (routine use of skin moisturizers and/or emollients), bleach bath or soaks (for limited areas only), avoidance of central lines (particularly for erythrodermic patients) and prophylactic use of mupirocin in cases of *Staphylococcus aureus* (*S. aureus*) colonization. Patients with MF/SS undergoing treatment with alemtuzumab-containing regimens should be closely monitored for cytomegalovirus (CMV) reactivation and preemptively treated with antivirals to avoid overt CMV disease (see Guidelines section for Supportive Care for NHL).

For active or suspected infection in patients with erythroderma, cultures from skin swab and nares (nostrils) should be taken to evaluate for *S. aureus* colonization/infection. Bleach baths or soaks may be helpful if the affected area is limited. Antimicrobial treatments may include intranasal mupirocin and/or oral dicloxacillin or cephalexin. For cases of suspected methicillin-resistant *S. aureus* (MRSA) infection, trimethoprim/sulfamethoxazole (TMP/SMX) or doxycycline should be considered. If no improvements in infection status are observed with the above agents, or if bacteremia is suspected, vancomycin should be initiated. Further information on the appropriate use of vancomycin is included in the NCCN Guidelines for the Prevention and Treatment of Cancer-related Infections (also available at nccn.org).

Infection with Gram-negative rods is common in necrotic tumors, and may lead to serious complications such as bacteremia/sepsis. For active or suspected infections in patients with ulcerated and necrotic tumors, blood cultures should be obtained and empiric therapy with antibacterials should be considered even in the absence of a fever. An

antimicrobial agent with broad-spectrum coverage (including coverage for both Gram-negative rods and Gram-positive cocci) should be chosen initially. The role of skin/wound culture is not clear in this setting. Further information on empiric therapy in cancer patients at risk for infections is included in the NCCN Guidelines for the Prevention and Treatment of Cancer-related Infections (at nccn.org).

References

1. Bradford PT, Devesa SS, Anderson WF, Toro JR. Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases. Blood 2009;113:5064-5073. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19279331.

2. Criscione VD, Weinstock MA. Incidence of cutaneous T-cell lymphoma in the United States, 1973-2002. Arch Dermatol 2007;143:854-859. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17638728.

3. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005;105:3768-3785. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15692063.

4. Vergier B, de Muret A, Beylot-Barry M, et al. Transformation of mycosis fungoides: clinicopathological and prognostic features of 45 cases. French Study Group of Cutaneious Lymphomas. Blood 2000;95:2212-2218. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10733487.

5. Diamandidou E, Colome-Grimmer M, Fayad L, et al. Transformation of mycosis fungoides/Sezary syndrome: clinical characteristics and prognosis. Blood 1998;92:1150-1159. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9694702.

6. Arulogun SO, Prince HM, Ng J, et al. Long-term outcomes of patients with advanced-stage cutaneous T-cell lymphoma and large cell transformation. Blood 2008;112:3082-3087. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18647960.

7. Benner MF, Jansen PM, Vermeer MH, Willemze R. Prognostic factors in transformed mycosis fungoides: a retrospective analysis of 100 cases. Blood 2012;119:1643-1649. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22160616.

8. Agar NS, Wedgeworth E, Crichton S, et al. Survival outcomes and prognostic factors in mycosis fungoides/Sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. J Clin Oncol 2010;28:4730-4739. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20855822.

9. de Coninck EC, Kim YH, Varghese A, Hoppe RT. Clinical characteristics and outcome of patients with extracutaneous mycosis fungoides. J Clin Oncol 2001;19:779-784. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11157031.

10. Kim YH, Bishop K, Varghese A, Hoppe RT. Prognostic factors in erythrodermic mycosis fungoides and the Sezary syndrome. Arch Dermatol 1995;131:1003-1008. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7661601.

11. Kim YH, Chow S, Varghese A, Hoppe RT. Clinical characteristics and long-term outcome of patients with generalized patch and/or plaque (T2) mycosis fungoides. Arch Dermatol 1999;135:26-32. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9923777.

12. Kim YH, Liu HL, Mraz-Gernhard S, et al. Long-term outcome of 525 patients with mycosis fungoides and Sezary syndrome: clinical prognostic factors and risk for disease progression. Arch Dermatol 2003;139:857-866. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12873880.

13. Vidulich KA, Talpur R, Bassett RL, Duvic M. Overall survival in erythrodermic cutaneous T-cell lymphoma: an analysis of prognostic factors in a cohort of patients with erythrodermic cutaneous T-cell lymphoma. Int J Dermatol 2009;48:243-252. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19261011.

14. Talpur R, Singh L, Daulat S, et al. Long-term outcomes of 1,263 patients with mycosis fungoides and Sezary syndrome from 1982 to 2009. Clin Cancer Res 2012;18:5051-5060. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22850569.

15. Pimpinelli N, Olsen EA, Santucci M, et al. Defining early mycosis fungoides. J Am Acad Dermatol 2005;53:1053-1063. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16310068.

16. Kim EJ, Hess S, Richardson SK, et al. Immunopathogenesis and therapy of cutaneous T cell lymphoma. J Clin Invest 2005;115:798-812. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15841167.

17. Thurber SE, Zhang B, Kim YH, et al. T-cell clonality analysis in biopsy specimens from two different skin sites shows high specificity in the diagnosis of patients with suggested mycosis fungoides. J Am Acad Dermatol 2007;57:782-790. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17646032.

18. Zhang B, Beck AH, Taube JM, et al. Combined use of PCR-based TCRG and TCRB clonality tests on paraffin-embedded skin tissue in the differential diagnosis of mycosis fungoides and inflammatory dermatoses. J Mol Diagn 2010;12:320-327. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20203005.

19. Mycosis fungoides cooperative study. Arch Dermatol 1975;111:457-459. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1079128.

20. Olsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110:1713-1722. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17540844.

21. Olsen EA, Whittaker S, Kim YH, et al. Clinical end points and response criteria in mycosis fungoides and Sezary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. J Clin Oncol 2011;29:2598-2607. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21576639.

22. Tsai EY, Taur A, Espinosa L, et al. Staging accuracy in mycosis fungoides and sezary syndrome using integrated positron emission tomography and computed tomography. Arch Dermatol 2006;142:577-584. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16702495.

23. Lynch JW, Jr., Linoilla I, Sausville EA, et al. Prognostic implications of evaluation for lymph node involvement by T-cell antigen receptor gene rearrangement in mycosis fungoides. Blood 1992;79:3293-3299. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1596570.

24. Hymes KB. Choices in the treatment of cutaneous T-cell lymphoma. Oncology (Williston Park) 2007;21:18-23. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17474355.

25. Keehn CA, Belongie IP, Shistik G, et al. The diagnosis, staging, and treatment options for mycosis fungoides. Cancer Control 2007;14:102-111. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17387295.

26. Rosen ST, Querfeld C. Primary Cutaneous T-Cell Lymphomas. Hematology 2006:323-330. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17124079.

27. Zackheim HS. Treatment of patch-stage mycosis fungoides with topical corticosteroids. Dermatol Ther 2003;16:283-287. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14686970.

28. Zackheim HS, Kashani-Sabet M, Amin S. Topical corticosteroids for mycosis fungoides. Experience in 79 patients. Arch Dermatol 1998;134:949-954. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9722724.

29. Zackheim HS. Topical carmustine (BCNU) in the treatment of mycosis fungoides. Dermatol Ther 2003;16:299-302. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14686972.

30. Kim YH. Management with topical nitrogen mustard in mycosis fungoides. Dermatol Ther 2003;16:288-298. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14686971.

31. Kim YH, Martinez G, Varghese A, Hoppe RT. Topical nitrogen mustard in the management of mycosis fungoides: update of the Stanford experience. Arch Dermatol 2003;139:165-173. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12588222.

32. Lessin SR, Duvic M, Guitart J, et al. Topical chemotherapy in cutaneous T-cell lymphoma: positive results of a randomized, controlled, multicenter trial testing the efficacy and safety of a novel mechlorethamine, 0.02%, gel in mycosis fungoides. JAMA Dermatol 2013;149:25-32. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23069814.

33. Breneman D, Duvic M, Kuzel T, et al. Phase 1 and 2 trial of bexarotene gel for skin-directed treatment of patients with cutaneous T-cell lymphoma. Arch Dermatol 2002;138:325-332. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11902983.

34. Heald P, Mehlmauer M, Martin AG, et al. Topical bexarotene therapy for patients with refractory or persistent early-stage cutaneous T-cell lymphoma: results of the phase III clinical trial. J Am Acad Dermatol 2003;49:801-815. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14576658.

35. Apisarnthanarax N, Talpur R, Ward S, et al. Tazarotene 0.1% gel for refractory mycosis fungoides lesions: an open-label pilot study. J Am Acad Dermatol 2004;50:600-607. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15034511.

36. Coors EA, Schuler G, Von Den Driesch P. Topical imiquimod as treatment for different kinds of cutaneous lymphoma. Eur J Dermatol 2006;16:391-393. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16935796.

37. Deeths MJ, Chapman JT, Dellavalle RP, et al. Treatment of patch and plaque stage mycosis fungoides with imiquimod 5% cream. J Am Acad Dermatol 2005;52:275-280. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15692473.

38. Martinez-Gonzalez MC, Verea-Hernando MM, Yebra-Pimentel MT, et al. Imiquimod in mycosis fungoides. Eur J Dermatol 2008;18:148-152. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18424373.

39. Hoppe RT. Mycosis fungoides: radiation therapy. Dermatol Ther 2003;16:347-354. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14686978.

40. Wilson LD, Kacinski BM, Jones GW. Local superficial radiotherapy in the management of minimal stage IA cutaneous T-cell lymphoma (Mycosis Fungoides). Int J Radiat Oncol Biol Phys 1998;40:109-115. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9422565.

41. Micaily B, Miyamoto C, Kantor G, et al. Radiotherapy for unilesional mycosis fungoides. Int J Radiat Oncol Biol Phys 1998;42:361-364. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9788416.

42. Ysebaert L, Truc G, Dalac S, et al. Ultimate results of radiation therapy for T1-T2 mycosis fungoides (including reirradiation). Int J Radiat Oncol Biol Phys 2004;58:1128-1134. Available at: http://www.ncbi.nlm.nih.gov/PubMed/15001254.

43. Chinn DM, Chow S, Kim YH, Hoppe RT. Total skin electron beam therapy with or without adjuvant topical nitrogen mustard or nitrogen mustard alone as initial treatment of T2 and T3 mycosis fungoides. Int J Radiat Oncol Biol Phys 1999;43:951-958. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10192339.

44. Harrison C, Young J, Navi D, et al. Revisiting low-dose total skin electron beam therapy in mycosis fungoides. Int J Radiat Oncol Biol Phys 2011;81:e651-657. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21489711.

45. Kamstrup MR, Lindahl LM, Gniadecki R, et al. Low-dose total skin electron beam therapy as a debulking agent for cutaneous T-cell lymphoma: an open-label prospective phase II study. Br J Dermatol 2012;166:399-404. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21967035.

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46. Diederen PV, van Weelden H, Sanders CJ, et al. Narrowband UVB and psoralen-UVA in the treatment of early-stage mycosis fungoides: a retrospective study. J Am Acad Dermatol 2003;48:215-219. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12582391.

47. Gathers RC, Scherschun L, Malick F, et al. Narrowband UVB phototherapy for early-stage mycosis fungoides. J Am Acad Dermatol 2002;47:191-197. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12140464.

48. Ponte P, Serrao V, Apetato M. Efficacy of narrowband UVB vs. PUVA in patients with early-stage mycosis fungoides. J Eur Acad Dermatol Venereol 2010;24:716-721. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19929938.

49. Querfeld C, Rosen ST, Kuzel TM, et al. Long-term follow-up of patients with early-stage cutaneous T-cell lymphoma who achieved complete remission with psoralen plus UV-A monotherapy. Arch Dermatol 2005;141:305-311. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15781671.

50. Edelson R, Berger C, Gasparro F, et al. Treatment of cutaneous T-cell lymphoma by extracorporeal photochemotherapy. Preliminary results. N Engl J Med 1987;316:297-303. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3543674.

51. Zic JA. The treatment of cutaneous T-cell lymphoma with photopheresis. Dermatol Ther 2003;16:337-346. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14686977.

52. Zic JA, Stricklin GP, Greer JP, et al. Long-term follow-up of patients with cutaneous T-cell lymphoma treated with extracorporeal photochemotherapy. J Am Acad Dermatol 1996;35:935-945. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8959953.

53. Gottlieb SL, Wolfe JT, Fox FE, et al. Treatment of cutaneous T-cell lymphoma with extracorporeal photopheresis monotherapy and in combination with recombinant interferon alfa: a 10-year experience at a single institution. J Am Acad Dermatol 1996;35:946-957. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8959954.

54. Bisaccia E, Gonzalez J, Palangio M, et al. Extracorporeal photochemotherapy alone or with adjuvant therapy in the treatment of cutaneous T-cell lymphoma: a 9-year retrospective study at a single institution. J Am Acad Dermatol 2000;43:263-271. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10906649.

55. Olsen EA. Interferon in the treatment of cutaneous T-cell lymphoma. Dermatol Ther 2003;16:311-321. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14686974.

56. Zhang C, Duvic M. Treatment of cutaneous T-cell lymphoma with retinoids. Dermatol Ther 2006;19:264-271. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17014481.

57. Kaplan EH, Rosen ST, Norris DB, et al. Phase II study of recombinant human interferon gamma for treatment of cutaneous T-cell lymphoma. J Natl Cancer Inst 1990;82:208-212. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2104937.

58. Duvic M, Hymes K, Heald P, et al. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. J Clin Oncol 2001;19:2456-2471. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11331325.

59. Duvic M, Martin AG, Kim Y, et al. Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. Arch Dermatol 2001;137:581-593. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11346336.

60. Querfeld C, Rosen ST, Guitart J, et al. Comparison of selective retinoic acid receptor- and retinoic X receptor-mediated efficacy, tolerance, and survival in cutaneous t-cell lymphoma. J Am Acad Dermatol 2004;51:25-32. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15243520.

61. Duvic M, Talpur R, Ni X, et al. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). Blood 2007;109:31-39. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16960145.

62. Olsen EA, Kim YH, Kuzel TM, et al. Phase IIB multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. J Clin Oncol 2007;25:3109-3115. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17577020.

63. Demierre M, Whittaker S, Kim Y, et al. Pooled analyses of two international, multicenter clinical studies of romidepsin in 167 patients with cutaneous T-cell lymphoma (CTCL) [abstract]. J Clin Oncol 2009;27:Abstract 8546. Available at: http://meeting.ascopubs.org/cgi/content/abstract/27/15S/8546.

64. Kim Y, Whittaker S, Demierre MF, et al. Clinically significant responses achieved with romidepsin in treatment-refractory cutaneous T-cell lymphoma: final results from a Phase 2B, international, multicenter, registration study [abstract]. Blood 2008;112:Abstract 263. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/112/11/263.

65. Duvic M, Olsen EA, Breneman D, et al. Evaluation of the long-term tolerability and clinical benefit of vorinostat in patients with advanced cutaneous T-cell lymphoma. Clin Lymphoma Myeloma 2009;9:412-416. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19951879.

66. Piekarz R, Wright J, Frye R, et al. Final results of a phase 2 NCI multicenter study of romidepsin in patients with relapsed peripheral T-cell lymphoma (PTCL) [abstract]. Blood 2009;114:Abstract 1657. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/114/22/1657.

67. Whittaker SJ, Demierre MF, Kim EJ, et al. Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. J Clin Oncol 2010;28:4485-4491. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20697094.

68. Piekarz RL, Frye R, Turner M, et al. Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma. J Clin Oncol 2009;27:5410-5417. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19826128.

69. Kim YH, Demierre MF, Kim EJ, et al. Clinically significant responses achieved with romidepsin in 37 patient with cutaneous T-cell lymphoma (CTCL) with blood involvement [abstract]. Blood 2009;114:Abstract 2683. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/114/22/2683.

70. Olsen E, Duvic M, Frankel A, et al. Pivotal phase III trial of two dose levels of denileukin diftitox for the treatment of cutaneous T-cell lymphoma. J Clin Oncol 2001;19:376-388. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11208829.

71. Prince HM, Duvic M, Martin A, et al. Phase III placebo-controlled trial of denileukin diftitox for patients with cutaneous T-cell lymphoma. J Clin Oncol 2010;28:1870-1877. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20212249.

72. Zackheim HS, Kashani-Sabet M, Hwang ST. Low-dose methotrexate to treat erythrodermic cutaneous T-cell lymphoma: results in twenty-nine patients. J Am Acad Dermatol 1996;34:626-631. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8601652.

73. Zackheim HS, Kashani-Sabet M, McMillan A. Low-dose methotrexate to treat mycosis fungoides: a retrospective study in 69 patients. J Am Acad Dermatol 2003;49:873-878. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14576667.

74. Duvic M, Talpur R, Wen S, et al. Phase II evaluation of gemcitabine monotherapy for cutaneous T-cell lymphoma. Clin Lymphoma Myeloma 2006;7:51-58. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16879770.

75. Marchi E, Alinari L, Tani M, et al. Gemcitabine as frontline treatment for cutaneous T-cell lymphoma: phase II study of 32 patients. Cancer

2005;104:2437-2441. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/16216001.

76. Zinzani PL, Baliva G, Magagnoli M, et al. Gemcitabine treatment in pretreated cutaneous T-cell lymphoma: experience in 44 patients. J Clin Oncol 2000;18:2603-2606. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/10893292.

77. Zinzani PL, Venturini F, Stefoni V, et al. Gemcitabine as single agent in pretreated T-cell lymphoma patients: evaluation of the long-term outcome. Ann Oncol 2010;21:860-863. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/19887465.

78. Cummings FJ, Kim K, Neiman RS, et al. Phase II trial of pentostatin in refractory lymphomas and cutaneous T-cell disease. J Clin Oncol 1991;9:565-571. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/2066753.

79. Foss FM, Ihde DC, Breneman DL, et al. Phase II study of pentostatin and intermittent high-dose recombinant interferon alfa-2a in advanced mycosis fungoides/Sezary syndrome. J Clin Oncol 1992;10:1907-1913. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/1453206.

80. Tsimberidou AM, Giles F, Romaguera J, et al. Activity of interferon-alpha and isotretinoin in patients with advanced, refractory lymphoid malignancies. Cancer 2004;100:574-580. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/14745875.

81. Tani M, Fina M, Alinari L, et al. Phase II trial of temozolomide in patients with pretreated cutaneous T-cell lymphoma. Haematologica 2005;90:1283-1284. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/16154858.

82. Zinzani PL, Musuraca G, Tani M, et al. Phase II trial of proteasome inhibitor bortezomib in patients with relapsed or refractory cutaneous T-cell lymphoma. J Clin Oncol 2007;25:4293-4297. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/17709797.

83. Wollina U, Dummer R, Brockmeyer NH, et al. Multicenter study of pegylated liposomal doxorubicin in patients with cutaneous T-cell lymphoma. Cancer 2003;98:993-1001. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/12942567.

84. Pulini S, Rupoli S, Goteri G, et al. Pegylated liposomal doxorubicin in the treatment of primary cutaneous T-cell lymphomas. Haematologica 2007;92:686-689. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/17488695.

85. Quereux G, Marques S, Nguyen JM, et al. Prospective multicenter study of pegylated liposomal doxorubicin treatment in patients with advanced or refractory mycosis fungoides or Sezary syndrome. Arch Dermatol 2008;144:727-733. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/18559761.

86. Dummer R, Quaglino P, Becker JC, et al. Prospective international multicenter phase II trial of intravenous pegylated liposomal doxorubicin monochemotherapy in patients with stage IIB, IVA, or IVB advanced mycosis fungoides: final results from EORTC 21012. J Clin Oncol 2012;30:4091-4097. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/23045580.

87. Straus DJ, Duvic M, Horwitz SM, et al. Final Results of Phase II Trial of Pegylated Liposomal Doxorubicin (PLD) Followed by Bexarotene (Bex) in Advanced Cutaneous T-Cell Lymphoma (CTCL) [abstract]. Blood 2011;118:Abstract 882. Available at:
http://abstracts.hematologylibrary.org/cgi/content/abstract/118/21/882.

88. Horwitz SM, Kim YH, Foss F, et al. Identification of an active, well-tolerated dose of pralatrexate in patients with relapsed or refractory cutaneous T-cell lymphoma (CTCL). Blood 2012. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/22394596.

89. Talpur R, Jones DM, Alencar AJ, et al. CD25 expression is correlated with histological grade and response to denileukin diftitox in cutaneous T-cell lymphoma. J Invest Dermatol 2006;126:575-583. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16410787.

90. Awar O, Duvic M. Treatment of transformed mycosis fungoides with intermittent low-dose gemcitabine. Oncology 2007;73:130-135. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18337626.

91. Foss F, Horwitz SM, Coiffier B, et al. Pralatrexate is an effective treatment for relapsed or refractory transformed mycosis fungoides: a subgroup efficacy analysis from the PROPEL study. Clin Lymphoma Myeloma Leuk 2012;12:238-243. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22542448.

92. O'Connor OA, Pro B, Pinter-Brown L, et al. Pralatrexate in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma: Results From the Pivotal PROPEL Study. J Clin Oncol 2011;29:1182-1189. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21245435.

93. Roenigk HH, Jr., Kuzel TM, Skoutelis AP, et al. Photochemotherapy alone or combined with interferon alpha-2a in the treatment of cutaneous T-cell lymphoma. J Invest Dermatol 1990;95:198S-205S. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2258636.

94. Rupoli S, Goteri G, Pulini S, et al. Long-term experience with low-dose interferon-alpha and PUVA in the management of early mycosis fungoides. Eur J Haematol 2005;75:136-145. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16000130.

95. McGinnis KS, Shapiro M, Vittorio CC, et al. Psoralen plus long-wave UV-A (PUVA) and bexarotene therapy: An effective and synergistic combined adjunct to therapy for patients with advanced cutaneous T-cell lymphoma. Arch Dermatol 2003;139:771-775. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12810509.

96. Kuzel TM, Roenigk HH, Jr., Samuelson E, et al. Effectiveness of interferon alfa-2a combined with phototherapy for mycosis fungoides and the Sezary syndrome. J Clin Oncol 1995;13:257-263. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7799028.

97. Stadler R, Otte HG, Luger T, et al. Prospective randomized multicenter clinical trial on the use of interferon -2a plus acitretin versus interferon -2a plus PUVA in patients with cutaneous T-cell lymphoma stages I and II. Blood 1998;92:3578-3581. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9808550.

98. Suchin KR, Cucchiara AJ, Gottleib SL, et al. Treatment of cutaneous T-cell lymphoma with combined immunomodulatory therapy: a 14-year experience at a single institution. Arch Dermatol 2002;138:1054-1060. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12164743.

99. Chiarion-Sileni V, Bononi A, Fornasa CV, et al. Phase II trial of interferon-alpha-2a plus psolaren with ultraviolet light A in patients with cutaneous T-cell lymphoma. Cancer 2002;95:569-575. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12209749.

100. Rupoli S, Pimpinelli N, Goteri G, et al. Low Dose Bexarotene and Ultraviolet A Photochemotherapy (PUVA) In a Prospective Phase II Clinical Study for Refractory and/or Resistant Cutaneous T Cell Lymphomas (CTCL) [abstract]. Blood 2010;116:Abstract 3953. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/3953.

101. Whittaker S, Ortiz P, Dummer R, et al. Efficacy and safety of bexarotene combined with psoralen-ultraviolet A (PUVA) compared with PUVA treatment alone in stage IB-IIA mycosis fungoides: final results from the EORTC Cutaneous Lymphoma Task Force phase III randomized clinical trial (NCT00056056). Br J Dermatol 2012;167:678-687. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22924950.

102. Raphael BA, Shin DB, Suchin KR, et al. High clinical response rate of Sezary syndrome to immunomodulatory therapies: prognostic markers of response. Arch Dermatol 2011;147:1410-1415. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21844430.

103. McGinnis KS, Junkins-Hopkins JM, Crawford G, et al. Low-dose oral bexarotene in combination with low-dose interferon alfa in the treatment of cutaneous T-cell lymphoma: clinical synergism and

possible immunologic mechanisms. J Am Acad Dermatol 2004;50:375-379. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14988678.

104. Straus DJ, Duvic M, Kuzel T, et al. Results of a phase II trial of oral bexarotene (Targretin) combined with interferon alfa-2b (Intron-A) for patients with cutaneous T-cell lymphoma. Cancer 2007;109:1799-1803. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17366595.

105. Foss F, Demierre MF, DiVenuti G. A phase-1 trial of bexarotene and denileukin diftitox in patients with relapsed or refractory cutaneous T-cell lymphoma. Blood 2005;106:454-457. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15811959.

106. Duvic M, Apisarnthanarax N, Cohen DS, et al. Analysis of long-term outcomes of combined modality therapy for cutaneous T-cell lymphoma. J Am Acad Dermatol 2003;49:35-49. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12833006.

107. Duarte RF, Schmitz N, Servitje O, Sureda A. Haematopoietic stem cell transplantation for patients with primary cutaneous T-cell lymphoma. Bone Marrow Transplant 2008;41:597-604. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18176611.

108. Burt RK, Guitart J, Traynor A, et al. Allogeneic hematopoietic stem cell transplantation for advanced mycosis fungoides: evidence of a graft-versus-tumor effect. Bone Marrow Transplant 2000;25:111-113. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10654025.

109. Kahata K, Hashino S, Takahata M, et al. Durable remission of Sezary syndrome after unrelated bone marrow transplantation by reduced-intensity conditioning. Acta Haematol 2008;120:14-18. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18716396.

110. Masood N, Russell KJ, Olerud JE, et al. Induction of complete remission of advanced stage mycosis fungoides by allogeneic hematopoietic stem cell transplantation. J Am Acad Dermatol 2002;47:140-145. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12077596.

111. Tsuji H, Wada T, Murakami M, et al. Two cases of mycosis fungoides treated by reduced-intensity cord blood transplantation. J Dermatol 2010;37:1040-1045. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21083707.

112. Duarte RF, Canals C, Onida F, et al. Allogeneic hematopoietic cell transplantation for patients with mycosis fungoides and Sezary syndrome: a retrospective analysis of the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 2010;28:4492-4499. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20697072.

113. Duvic M, Donato M, Dabaja B, et al. Total skin electron beam and non-myeloablative allogeneic hematopoietic stem-cell transplantation in advanced mycosis fungoides and Sezary syndrome. J Clin Oncol 2010;28:2365-2372. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20351328.

114. Molina A, Zain J, Arber DA, et al. Durable clinical, cytogenetic, and molecular remissions after allogeneic hematopoietic cell transplantation for refractory Sezary syndrome and mycosis fungoides. J Clin Oncol 2005;23:6163-6171. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16135483.

115. Wu PA, Kim YH, Lavori PW, et al. A meta-analysis of patients receiving allogeneic or autologous hematopoietic stem cell transplant in mycosis fungoides and Sezary syndrome. Biol Blood Marrow Transplant 2009;15:982-990. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19589488.

116. Lundin J, Hagberg H, Repp R, et al. Phase 2 study of alemtuzumab (anti-CD52 monoclonal antibody) in patients with advanced mycosis fungoides/Sezary syndrome. Blood 2003;101:4267-4272. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12543862.

117. Alinari L, Geskin L, Grady T, et al. Subcutaneous alemtuzumab for Sezary Syndrome in the very elderly. Leuk Res 2008;32:1299-1303. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18096224.

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118. Bernengo MG, Quaglino P, Comessatti A, et al. Low-dose intermittent alemtuzumab in the treatment of Sezary syndrome: clinical and immunologic findings in 14 patients. Haematologica 2007;92:784-794. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17550851.

119. Zinzani PL, Alinari L, Tani M, et al. Preliminary observations of a phase II study of reduced-dose alemtuzumab treatment in patients with pretreated T-cell lymphoma. Haematologica 2005;90:702-703. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15921394.

120. Gautschi O, Blumenthal N, Streit M, et al. Successful treatment of chemotherapy-refractory Sezary syndrome with alemtuzumab (Campath-1H). Eur J Haematol 2004;72:61-63. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14962265.

121. Kennedy GA, Seymour JF, Wolf M, et al. Treatment of patients with advanced mycosis fungoides and Sezary syndrome with alemtuzumab. Eur J Haematol 2003;71:250-256. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12950233.

122. Querfeld C, Mehta N, Rosen ST, et al. Alemtuzumab for relapsed and refractory erythrodermic cutaneous T-cell lymphoma: a single institution experience from the Robert H. Lurie Comprehensive Cancer Center. Leuk Lymphoma 2009;50:1969-1976. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19860617.

123. Demierre MF, Gan S, Jones J, Miller DR. Significant impact of cutaneous T-cell lymphoma on patients' quality of life: results of a 2005 National Cutaneous Lymphoma Foundation Survey. Cancer 2006;107:2504-2511. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17048251.

124. Sampogna F, Frontani M, Baliva G, et al. Quality of life and psychological distress in patients with cutaneous lymphoma. Br J Dermatol 2009;160:815-822. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19120325.

125. Meyer N, Paul C, Misery L. Pruritus in cutaneous T-cell lymphomas: frequent, often severe and difficult to treat. Acta Derm Venereol 2010;90:12-17. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20107719.

126. Trautinger F, Knobler R, Willemze R, et al. EORTC consensus recommendations for the treatment of mycosis fungoides/Sezary syndrome. Eur J Cancer 2006;42:1014-1030. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16574401.

127. Demierre MF, Taverna J. Mirtazapine and gabapentin for reducing pruritus in cutaneous T-cell lymphoma. J Am Acad Dermatol 2006;55:543-544. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16908377.

128. Booken N, Heck M, Nicolay JP, et al. Oral aprepitant in the therapy of refractory pruritus in erythrodermic cutaneous T-cell lymphoma. Br J Dermatol 2011;164:665-667. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21039410.

129. Duval A, Dubertret L. Aprepitant as an antipruritic agent? N Engl J Med 2009;361:1415-1416. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19797294.

130. Bigliardi PL, Stammer H, Jost G, et al. Treatment of pruritus with topically applied opiate receptor antagonist. J Am Acad Dermatol 2007;56:979-988. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17320241.

131. Brune A, Metze D, Luger TA, Stander S. [Antipruritic therapy with the oral opioid receptor antagonist naltrexone. Open, non-placebo controlled administration in 133 patients]. Hautarzt 2004;55:1130-1136. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15517116.

132. Metze D, Reimann S, Beissert S, Luger T. Efficacy and safety of naltrexone, an oral opiate receptor antagonist, in the treatment of pruritus in internal and dermatological diseases. J Am Acad Dermatol

1999;41:533-539. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/10495371.

133. Axelrod PI, Lorber B, Vonderheid EC. Infections complicating
mycosis fungoides and Sezary syndrome. JAMA 1992;267:1354-1358.
Available at: http://www.ncbi.nlm.nih.gov/pubmed/1740857.

Adult T-cell Leukemia/Lymphoma

Adult T-cell leukemia/lymphoma (ATLL) is a type of peripheral T-cell malignancy caused by a retrovirus, the human T-cell lymphotropic virus type I (HTLV-1), and is associated with a long period of latency (often manifesting several decades after exposure).[1,2] ATLL is endemic to several regions, including southwest regions in Japan, the Caribbean, and parts of central Africa, owing to the distribution of HTLV-1.[1-3] In the International Peripheral T-cell Lymphoma (PTCL) Project, ATLL comprised about 10% of the diagnosis for confirmed cases of PTCL or NK/T-cell lymphomas (N=1,153).[4] ATLL was rare in North America or Europe (≤2%), but prevalent in Asia (25%), with all cases from Asia originating in Japan. Among HTLV-1 carriers in Japan, the cumulative life-time risk of developing ATLL is estimated to be 2.5%; the annual incidence of ATLL in Japan is approximately 700.[2]

ATLL can be associated with an aggressive disease course, with median overall survival (OS) of 6 to 10 months among patients with the acute or lymphoma subtypes.[4-6] The Lymphoma Study Group of the Japan Clinical Oncology Group (JCOG) have classified ATLL into four subtypes (smoldering, chronic, acute, or lymphoma) based on laboratory evaluations (e.g., serum lactate dehydrogenase [LDH], calcemia, lymphocytosis) and clinical features of ATLL (e.g., lymphadenopathy, hepatosplenomegaly, skin involvement).[6] The smoldering and chronic subtypes are considered indolent forms of ATLL. Both subtypes are usually characterized by 5% or more abnormal T-lymphocytes in the peripheral blood and may have skin or pulmonary lesions (but no ascites or pleural effusion). In addition, the smoldering subtype is associated with a normal lymphocyte count, normal serum calcium level, LDH levels within 1.5 times upper normal limit, and no involvement of liver, spleen, CNS, bone, or gastrointestinal (GI) tract.[6] The expected median OS for this subtype generally exceeds 5 years.[2]

The chronic subtype is characterized by absolute lymphocytosis (≥4 x 10^9/L) with T-lymphocytes ≥3.5 x 10^9/L, normal calcium level, LDH levels within 2 times upper normal limit, and no involvement of CNS, bone or GI tract; lymphadenopathy and involvement of liver and spleen may be present.[6] The lymphoma subtype is characterized by absence of lymphocytosis, ≤1% abnormal T-lymphocytes, and histologically-proven lymphadenopathy with or without extranodal lesions. The acute subtype usually presents with leukemic manifestation and tumour lesions, and represent cases that are not classified as any of the other 3 subtypes above.[6] The acute subtype is associated with a rapidly progressive disease course, and features including elevated LDH levels, hypercalcemia (with or without lytic bone lesions), B symptoms, generalized lymphadenopathy, splenomegaly, hepatomegaly, skin involvement, and organ infiltration.[1,2]

The smoldering and chronic subtypes have a more favorable prognosis compared with the acute or the lymphoma subtypes. In the analysis of patients with ATLL (N=818; mean age 57 years) from the Lymphoma Study Group of JCOG, the estimated 4-year OS rates for patients with acute, lymphoma, chronic, and smoldering subtypes were 5%, 6%, 27%, and 63%, respectively.[6] The median OS was 6, 10, 24 months, and not yet reached, respectively. The maximum duration of follow-up was 7 years in this study.[6] The analysis from the International PTCL Project confirmed the poor outcomes of patients with acute or lymphoma subtypes of ATLL, with a median OS of 10 months.[4] In a recent report from a long-term follow-up of patients with newly diagnosed indolent ATLL (N=90), the median OS was 4 years and the estimated 5-, 10-, and 15-year survival rates were 47%, 25%, and 14%, respectively.[7] In the subgroup analysis, the 15-year OS rate and median OS tended to be higher for the chronic subtype (15% and 5 years, respectively) than the smoldering subtype (13% and 3 years,

respectively). These long-term outcomes appear poorer than expected for patients with indolent ATLL; the heterogeneity in outcomes among patients with even the indolent subtype of the disease may be explained, in part, by differences in patient- and disease-related factors.

In patients with ATLL, poor performance status, elevated LDH level, ≥4 total involved lesions, hypercalcemia and age ≥40 years have been identified as major adverse prognostic factors based on data from a large number of patients.[2,8] Among patients with the chronic subtype, factors such as poor performance status, ≥4 total involved lesions, bone marrow involvement, elevated LDH, elevated blood urea nitrogen, and low albumin levels have been identified as potential prognostic factors for decreased survival.[2,7] Further studies with a larger number of patients are needed to elucidate prognostic factors that may help to further risk stratify patients with indolent ATLL. For patients with aggressive subtypes of ATLL, the International PTCL Project recently reported that the International Prognostic Index (IPI) was a useful model for predicting outcomes.[4] Based on univariate analysis, presence of B symptoms, platelet count <150 × 10^9/L, and high IPI score (≥3) were found to be associated with decreased OS. Based on multivariate analysis, however, IPI score was the only independent predictor for OS outcomes.[4] Recently, a report based on data from patients with ATLL in North America (N=89; acute or lymphoma subtypes in 79%) found that IPI scores were not always predictive for ATLL outcomes, and proposed a new prognostic model.[5] In this study, the investigators identified 3 prognostic categories based on the following factors: ECOG performance status, Ann Arbor stage, age, and serum calcium level at diagnosis.[5]

In the NCCN Guidelines, patients with ATLL are classified into 4 subtypes (chronic, smoldering, acute and lymphoma) according to the Shimoyama criteria.[6]

Diagnosis

The diagnosis of ATLL requires histopathology and immunophenotyping of tumor lesion, peripheral blood smear analysis for atypical cells, flow cytometry on peripheral blood and HTLV-1 serology.[9,10] The presence of ≥5% T-lymphocytes with an abnormal immunophenotype in the peripheral blood is required for the diagnosis of ATLL in patients without histologically proven tumor lesions.[6] The cytological features of ATLL may be broad, but typical ATLL cells are characterized by so-called 'flower cells', which show distinct polylobated nuclei with homogeneous and condensed chromatin, small or absent nucleoli, and agranular and basophilic cytoplasm.[1,10] These cytological characteristics are most evident in the acute subtype of the disease.[2] HTLV-1 serology should be assessed by ELISA, and if positive, a confirmed by western blot. If the result from western blot is indeterminate, then PCR analysis for HTLV-1 can be performed. Monoclonal integration of HTLV-1 proviral DNA occurs in all cases of ATLL; HTLV-1 integration patterns have been reported to have clinical and prognostic implications for ATLL.[11] Bone marrow biopsy or aspiration is generally not required to establish the diagnosis of ATLL. However, bone marrow evaluation may be useful as bone marrow involvement has been reported as an independent predictor of poor prognosis in ATLL.[12] If the diagnosis of ATLL is not established on peripheral blood examination, bone marrow biopsy or biopsy of the lymph nodes or lesions in skin or GI tract should be performed. Biopsy of the suspicious lesion may also help to rule out certain underlying infections (e.g., tuberculosis, histoplasmosis, and toxoplasmosis). Excisional biopsy is recommended instead of core needle biopsy for the lymph nodes.[10]

If a biopsy is performed, the immunophenotyping panel should at minimum include the following markers: CD3, CD4, CD7, CD8, and CD25. The typical immunophenotype in most patients with ATLL

involves mature CD4-positive T cells with expression of CD2, CD5, CD25, CD45RO, CD29, T-cell receptor αβ and HLA-DR.[1,10] Most ATLL cells lack CD7 and CD26 and have a dim CD3 expression.[10] In the Guidelines, the following is included as representative of a typical immunophenotype for ATLL: CD2+, CD3+, CD4+, CD7-, CD8-, CD25+, CD30-/+, TCR αβ+.

The clinical features of ATLL differ by subtype and disease stage, but patients with the most common acute or lymphoma subtypes may frequently present with lymphadenopathy (77%), fatigue (32%), anorexia (26%), skin eruptions (23%), abdominal pain (23%), pulmonary complications (18%; due to leukemic infiltration and/or infections), splenomegaly (13%), and hepatomegaly (10%).[2,4] Bone marrow involvement (28%) and CNS involvement (10%) are also not uncommon.[2,4]

Workup

The initial workup for ATLL should include a comprehensive physical examination with complete skin examination, and CT scans of the chest, abdomen and pelvis. Most patients with acute ATLL have elevated LDH levels, and lymphocytosis is found in patients with the acute or chronic type at presentation. Laboratory evaluations should include a complete blood count (CBC) and metabolic panel (serum electrolyte levels, calcium, creatinine and blood urea nitrogen), and measurement of serum LDH levels.

Upper GI tract endoscopy should be considered in selected cases since GI tract involvement is frequently observed in patients with aggressive ATLL.[13] CNS evaluation using CT scan, MRI and/or lumbar puncture may also be useful for all patients with acute or lymphoma subtypes or in patients with neurological manifestations.[14]

Response Criteria

The current response criteria used for ATLL are based on modifications to the original 1991 JCOG response criteria as suggested at the international consensus meeting. The modified response criteria reflect the widely used criteria for CLL and NHL, which were published in 1996 and 1999, respectively.[15,16] These response criteria are based on the normalization or reduction in the size of enlarged lymph nodes and extranodal masses (as calculated by the sum of the products of the greatest diameters of measurable disease), reduction in the size of spleen or liver and decrease in the involvement of peripheral blood, bone marrow and skin.[10] The response is categorized as a complete remission (CR; defined as complete disappearance of all clinical, microscopic, and radiographic evidence of disease and absolute lymphocyte count, including flower cells, <4 x 10^9/L in the peripheral blood), partial remission (PR; defined as ≥50% reduction in the sum of the products of the greatest diameters of measurable disease without the appearance of new lesions, no increase in spleen or liver size, ≥50% reduction in skin involvement, and ≥50% reduction in absolute lymphocyte counts in peripheral blood), stable disease (SD; failure to achieve CR or PR with no progressive disease) and relapsed disease or progressive disease (PD; new or ≥50% increase in lymph node lesions, extranodal mass, or splenomegaly/hepatomegaly, ≥50% increase in skin involvement, 50% increase from nadir in the count of flower cells and an increase in absolute lymphocyte count, including flower cells, of >4 x 10^9/L).[10] Each of the criterion for the response categories should be observed for a minimal period of 4 weeks to qualify for the response (e.g., CR, PR, SD). The response criteria also includes a category for unconfirmed CR, defined as ≥75% reduction in tumor size but with a residual mass after treatment, with an absolute lymphocyte count, including flower cells, of <4 x 10^9/L. The usefulness of PET or PET-CT

has not been evaluated in the response assessment of patients with ATLL.

Treatment Options

The ATLL subtype is an important factor for predicting prognosis and deciding appropriate treatment strategies. Smoldering and chronic subtypes are considered indolent, and are usually managed similarly to indolent NHL with watchful waiting until symptomatic disease. In contrast, the acute and lymphoma subtypes typically require immediate therapy.

A number of small studies and cases have reported on the activity of the combination of an anti-retroviral agent zidovudine and interferon (IFN)-alfa in patients with ATLL.[17-22] Among patients with primarily treatment-naïve aggressive ATLL, antiviral therapy with zidovudine and IFN-alfa resulted in overall response rate (ORR) of 58%-80% and CR rates of 20%-50%.[17-19] Outcomes with this therapy for previously treated patients with relapsed/refractory disease were poorer, with ORR 17%-67% (nearly all PRs).[21,22] The results of a meta-analysis on the use of zidovudine and IFN for patients with ATLL were recently reported by Bazarbachi et al (N=254).[23] Most of the patients (n=207 evaluable) in this analysis had the acute (47%) or lymphoma (41%) subtypes, with the remaining patients presenting with indolent disease. Patients had been treated with first-line antiviral therapy alone (n=75; comprising a combination of zidovudine and IFN-alfa in 97% of cases), chemotherapy alone (n=77; CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone] in 86% of cases) or chemotherapy followed by maintenance antiviral therapy (n=55). Among the patients who received first-line antiviral therapy alone, 60% had the acute subtype; in contrast, among the patients who received chemotherapy alone, 62% had the lymphoma subtype. In patients with available survival data and recorded

first-line therapy (n=207), the 5-year OS rates were 46%, 20% and 12%, respectively, for patients who received first-line antiviral therapy alone, chemotherapy alone and chemotherapy followed by antiviral therapy.[23] The ORR was 66% (CR in 35%) among patients who received first-line antiviral therapy (n=62 evaluable) and 88% (CR in 25%) among those who received first-line chemotherapy alone (n=48 evaluable). Among patients who received chemotherapy followed by antiviral therapy (n=14 evaluable), the ORR was 93% (CR in 50%).[23] For all patients with follow-up survival data (n=238), the median OS was 12 months and the 5-year OS rate was 23%. In the subgroup analysis by ATLL subtype, median OS was 6 months, 13 months, and not reached, respectively, in patients with acute, lymphoma and indolent (chronic or smoldering) subtypes; the 5-year OS rate was 15%, 16%, and 76%, respectively.[23] In the subgroup analysis by first-line treatment regimen, antiviral therapy resulted in significantly longer median OS (17 months vs. 12 months) and higher 5-year OS rate (46% vs. 14%) compared with chemotherapy (with or without maintenance antiviral therapy). Interestingly, only the patients with the acute and indolent subtype benefited significantly from first-line antiviral therapy, whereas patients with the lymphoma subtype had worse survival with antiviral therapy and better outcomes with first-line chemotherapy (with or without maintenance antiviral treatment). Multivariate analysis showed that only the ATLL subtype and type of first-line treatment were significant independent predictors for poorer OS.[23] These data suggest that antiviral therapy with zidovudine and IFN-alfa is effective in patients with leukemic ATLL, but not in the lymphoma subtype. A recent retrospective analysis evaluated outcomes in patients with aggressive ATLL (N=73; 60% had lymphoma subtype) treated with chemotherapy alone (n=39; primarily with CHOP-containing regimens) or combined therapy with chemotherapy and antiviral agents (zidovudine and INF-alfa; given concurrent or sequential to chemotherapy or deferred).[24] The

median OS among patients with the acute and lymphoma subtypes was 7.5 months and 10 months, respectively. The use of antiviral treatments (at any point on the study) was associated with significant OS benefit for both the subgroups with acute and lymphoma ATLL.[24] Among patients with the lymphoma subtype (n=32), treatment with first-line combination therapy (with chemotherapy and antiviral agents) or chemotherapy with deferred antivirals resulted in significant OS benefits compared with chemotherapy alone.[24]

In patients with ATLL, combination chemotherapy with CHOP has resulted in ORR of 64% to 88% and CR rates of 18% to 25%.[5,23,25] Median OS in published reports ranges from about 8 to 12 months.[23,25-27] In the aforementioned meta-analysis of data from patients with ATLL treated with first-line therapies, chemotherapy (primarily CHOP) alone resulted in median OS of 10 months and chemotherapy with or without maintenance antiviral therapy resulted in median OS of 12 months.[23] As alluded to earlier in the discussion, patients with the lymphoma subtype appeared to benefit more from first-line therapy with CHOP or CHOP-like chemotherapy (with or without maintenance antivirals) than with antivirals alone. In the subgroup of patients with the lymphoma subtype, OS outcome was significantly improved with first-line chemotherapy (n=72; median OS 16 months; 5-year OS 18%) compared with first-line antiviral treatment alone (n=13; median OS 7 months; 5-year OS 0%; *P*=0.009).[23] Several prospective studies have evaluated the role of more intensive chemotherapy combination regimens. A phase II multicenter study investigated the activity of CHOP followed by a regimen with etoposide, vindesine, ranimustine, mitoxantrone, and G-CSF in patients with ATLL (N=81).[28] The ORR with this intensive regimen was 74% (CR in 36%) and the median duration of response was 8 months. The median OS for all patients remained rather short, at 8.5 months; the 3-year OS rate was 13.5%.[28] In a small phase II trial

conducted by the AIDS Malignancy Consortium in patients with aggressive ATLL (N=19) , EPOCH chemotherapy followed by antiretroviral therapy (zidovudine, lamivudine, IFN-alfa up to 1 year) resulted in an ORR of 58% (CR in 10.5%) and a median duration of response of 13 months.[29] Although this regimen appeared to be active in this patient population, viral reactivation during therapy coincided with disease progression, which likely contributed to treatment failure.[29] A phase II trial by JCOG evaluated an intensive multidrug combination chemotherapy regimen comprising VCAP-AMP-VECP [vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP), doxorubicin, ranimustine, and prednisone (AMP), and vindesine, etoposide, carboplatin, and prednisone (VECP)], supported by G-CSF, in patients with aggressive ATLL (N=93).[30] The ORR with this regimen was 81% with a CR in 35.5% of patients. The median OS was 13 months and the estimated 2-year OS rate was 31%. Grade 4 neutropenia (65%) and thrombocytopenia (53%) were frequently observed despite the use of G-CSF.[30] Based on the promising results seen in this study, a randomized phase III trial was conducted by JCOG to evaluate first-line therapy with VCAP-AMP-VECP compared with biweekly CHOP (CHOP-14) in patients with aggressive ATLL (N=118).[25] The CR rate was significantly higher with VCAP-AMP-VECP compared with CHOP-14 (40% vs. 25%; *P*=0.02) but the 1-year PFS rate (28% vs. 16%) and 3-year OS rate (24% vs. 13%) were not significantly different. Median PFS (7 months vs. 5 months, respectively) and median OS (13 months vs. 11 months, respectively) were not different between treatment arms.[25] VCAP-AMP-VECP regimen was associated with higher incidence of toxicities compared with CHOP-14, including grade 4 neutropenia (98% vs. 83%), grade 4 thrombocytopenia (74% vs. 17%) and grade 3-4 infections (32% vs. 15%). Recently, a very limited number of ATLL cases have been treated with hyper-CVAD (hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and

dexamethasone), a regimen more commonly used in the treatment of patients with aggressive B-cell NHL and adult acute lymphoblastic leukemias.[31] Promising outcomes in terms of durable CRs have been reported with this regimen in two cases of ATLL[31]; however, prospective evaluations are needed.

Allogeneic HSCT (using myeloablative or non-myeloablative conditioning) may improve outcomes for some patients with ATLL,[32-37] with suggestion of a graft-versus-leukemia effect.[38,39] Studies with allogeneic HSCT (primarily using myeloablative conditioning) have reported promising disease-free and OS outcomes in patients with ATLL, with median leukemia-free survival exceeding 17 months and 3-year OS rate of about 45%.[33,35,37] However, the transplant procedure was associated with a high treatment-related mortality (TRM) rate of 40% to 63%.[33,35,37] In a multicenter retrospective analysis that evaluated outcomes in patients with aggressive ATLL who received myeloablative allogeneic HSCT (N=40), the median OS for all patients following transplant was about 10 months.[33] Acute graft-versus-host disease (GvHD) developed in 67% of patients. The estimated 3-year relapse-free survival and OS rate was 34% and 45%, respectively. The incidence of TRM was 42.5%, with early TRM (within 6 months of transplant) occurring in 13 patients (32.5%).[33] A large retrospective analysis was conducted in patients with ATLL who underwent allogeneic HSCT (related or unrelated) (N=386).[34] After a median follow up of 41 months, the 3-year OS rate for this patient cohort was 33%. Overall, the incidence of TRM was 43%, which was mainly due to infectious complications and organ failure. Based on multivariate analysis, patient age (>50 years), male sex, lack of a CR at the time of transplant, and the use of unrelated or cord blood were identified as adverse prognostic factors for OS outcomes.[34] In an effort to reduce the high rate of TRM observed with allogeneic HSCT, small

prospective studies have been conducted to evaluate the use of reduce-intensity conditioning (RIC) in allogeneic HSCT for patients with ATLL.[32,36] In a combined analysis from two clinical trials (N=29), the 5-year OS rate with RIC allogeneic HSCT was 34%.[32] The NRM rate was 27.5%; 11 patients died due to disease progression. Ten patients are alive at a median follow up of 82 months following transplant.[32]

A recent retrospective study evaluated the role of myeloablative conditioning and RIC allogeneic HSCT in a large group of patients with ATLL in Japan (N=586).[40] The majority of patients had either acute (57%) or lymphoma (28%)subtypes. Patients who received RIC for HSCT were older than those who received myeloablative conditioning regimens (median age 57 years vs. 49 years). The median OS (survival measured from time of HSCT) was 9.5 months among patients who received myeloablative conditioning, with a 3-year OS of 39%. For patients who received RIC, the median OS was 10 months, with a 3-year OS of 34%. The 3-year cumulative incidence of TRM was 38% with myeloablative conditioning and 33% with RIC. The 3-year cumulative incidence of ATLL-related death was 22.5% and 33%, respectively.[40] Based on multivariate analysis, older age (>55 years), male sex, lack of CR at time of HSCT, poorer performance status (PS ≥1), and unrelated donor HSCT were significant independent factors associated with decreased OS outcomes. Older age (>55 years) was a significant independent factor for poorer OS among patients who received myeloablative conditioning, but not for those who received RIC. In multivariate analysis, significant independent factors for risk of TRM included male sex, poorer performance status (PS ≥1), and unrelated donor HSCT; significant independent factors influencing risks for ATLL-related death included non-CR at time of HSCT, poor PS (PS ≥2), and RIC.[40] This analysis suggested that use of

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myeloablative conditioning or RIC resulted in similar outcomes with allogeneic HSCT, and that HSCT may offer long-term survival in some patients with ATLL. Prospective studies in larger groups of patients are warranted to further evaluate the role of allogeneic HSCT (with myeloablative conditioning or RIC) in the management of ATLL.

Patients with ATLL who relapse after allogeneic HSCT have poor prognosis and very limited treatment options. In a retrospective analysis of patients who progressed or relapsed after first allogeneic HSCT (N=35), donor lymphocyte infusion (DLI) was reported to induce long-term remissions in a few patients.[41] Most patients in this analysis received withdrawal of immunosuppression as the initial intervention. Among the patients who subsequently received DLI (n=9), the median OS after relapsed/progression was 17 months; the 3-year OS was 33%. Debulking of tumors (with dose-reduced CHOP or RT) prior to DLI seemed to be associated with improved outcomes; response was achieved in 5 of 6 patients who underwent pre-DLI cytoreductive therapy. DLI resulted in remission lasting more than 3 years in 3 of the patients.[41] Among the patients who did not receive DLI (n=26), the median OS was 4 months and the 3-year OS was 14%. The majority of these patients were treated with chemotherapy regimens following initial withdrawal of immunosuppression.[41] This analysis showed that induction of graft-versus-ATLL effect via treatments such as DLI may provide long-lasting remission in select patients with relapsed ATLL. However, prospective clinical trials are needed to confirm these findings.

NCCN Recommendations

There are no optimal standard treatment regimens for the management of ATLL. Thus, the NCCN Guidelines panel recommends enrollment in clinical trials as one of the options for all patients with ATLL. Prophylaxis

with anti-*Strongyloides* agents and prophylaxis with sulfamethoxazole-trimethoprim to prevent *Pneumocystis jirovecii* pneumonia are recommended for all patients undergoing treatment for ATLL.[10]

Primary Therapy

For patients with chronic or smoldering ATLL subtypes, observation is a valid option for asymptomatic cases since both of these subtypes are considered indolent diseases. Alternatively, if symptoms are present, these patients can be managed with skin-directed therapies (as recommend for patients with mycosis fungoides or Sézary syndrome within this NCCN Guidelines for NHL) for skin lesions, as appropriate, or with antiviral therapy with combination of zidovudine and IFN-alfa. As previously discussed, enrollment in suitable clinical trials is encouraged, where available.

For patients with acute ATLL, treatment options include participation in clinical trials, antiviral therapy with zidovudine and IFN-alfa, or combination chemotherapy regimens (i.e., CHOP, CHOEP, dose-adjusted EPOCH, or hyper-CVAD; all based on limited data only). For patients with the lymphoma subtype, primary treatment options include participation in clinical trials or combination chemotherapy (as mentioned above for acute ATLL); antiviral therapy alone is not considered effective for this group of patients.[23] CNS prophylaxis (with intrathecal methotrexate and cytarabine and corticosteroids) is recommended in patients with lymphoma subtype. No optimal treatment has been defined for these patients with aggressive ATLL and efficacy of long-term treatment is limited. As discussed earlier, allogeneic HSCT may be beneficial in some patients with ATLL.

Outside of a clinical trial, if a patient is not responding or is progressing, on antiviral treatment with zidovudine and IFN-alfa, treatment should be

stopped. If there is evidence of clinical benefit, treatment should continue until best response is achieved. The duration of initial therapy is usually 2 months. If life threatening manifestations occur, however, treatment can be discontinued before this period.

The optimal chemotherapy regimen for patients with ATLL is not yet established. The regimens listed in the NCCN Guidelines are based on institutional preferences and include CHOP, CHOEP, dose-adjusted EPOCH or hyper-CVAD.

Mogamulizumab (KW-0761) is a humanized monoclonal antibody approved for the treatment of patients with relapsed or refractory CCR4-positive ATLL in Japan. The approval was based on results of a multicenter phase II study for patients with relapsed, aggressive CCR4-positive ATLL (N=28).[42] The primary endpoint of the trial was ORR; the secondary endpoints included PFS and OS outcomes. Patients were treated with mogamulizumab IV 1 mg/kg once per week for 8 weeks, which was the dose derived from the phase I study.[43] The ORR among evaluable patients (n=26) was 50% (95% CI, 30–70%).[42] The median PFS and OS were approximately 5 months and 14 months, respectively. The most common adverse events included infusion reactions (89%) and skin rashes (63%).[42] Mogamulizumab is an investigational agent in the U.S. and has not been approved for any indication by the FDA. This agent is currently being evaluated in previously treated patients with ATLL in a multicenter open-label randomized study in the U.S. and elsewhere.

Response Assessment and Additional Therapy

For patients with chronic or smoldering ATLL who achieve an initial response (at 2 months following start of treatment; responders include those with a CR, uncertified PR, or PR), continuation of zidovudine and IFN-alfa is recommended. If the patient presents with persistent disease or has disease progression at 2 months from start of treatment (non-responders to initial therapy), options for additional therapy include participation in clinical trials, where available, or combination chemotherapy regimens (i.e., CHOP, EPOCH, or hyper-CVAD) or best supportive care. Allogeneic HSCT should be considered for patients with acute or lymphoma subtype.

For patients with acute or lymphoma ATLL subtypes who achieve an initial response to primary therapy, continuation of the prior therapy or allogeneic HSCT (if donor is available) are appropriate options. Patients with acute ATLL with persistent or progressive disease following primary therapy (non-responders) should be treated in the context of a clinical trial, where possible, best supportive care or an alternate regimen not previously used (under first-line therapy for ATLL, for second-line therapy recommended in the Guidelines for PTCL, or antiviral therapy with zidovudine and IFN). In non-responding patients with lymphoma ATLL subtypes after first-line therapy, options for second-line therapy include treatment in the context of a clinical trial, best supportive care or second-line therapy options based on the recommendations for PTCL. In patients with acute or lymphoma ATLL subtypes who achieve a response to second-therapy, allogeneic HSCT should be considered if a donor is available.

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References

1. Ohshima K, Jaffe ES, Kikuchi M. Adult T-cell leukemia/lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:281-284.

2. Tobinai K. Current management of adult T-cell leukemia/lymphoma. Oncology (Williston Park) 2009;23:1250-1256. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20120837.

3. Goncalves DU, Proietti FA, Ribas JG, et al. Epidemiology, treatment, and prevention of human T-cell leukemia virus type 1-associated diseases. Clin Microbiol Rev 2010;23:577-589. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20610824.

4. Suzumiya J, Ohshima K, Tamura K, et al. The International Prognostic Index predicts outcome in aggressive adult T-cell leukemia/lymphoma: analysis of 126 patients from the International Peripheral T-Cell Lymphoma Project. Ann Oncol 2009;20:715-721. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19150954.

5. Phillips AA, Shapira I, Willim RD, et al. A critical analysis of prognostic factors in North American patients with human T-cell lymphotropic virus type-1-associated adult T-cell leukemia/lymphoma: a multicenter clinicopathologic experience and new prognostic score. Cancer 2010;116:3438-3446. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20564100.

6. Shimoyama M. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the Lymphoma Study Group (1984-87). Br J Haematol 1991;79:428-437. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1751370.

7. Takasaki Y, Iwanaga M, Imaizumi Y, et al. Long-term study of indolent adult T-cell leukemia-lymphoma. Blood 2010;115:4337-4343. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20348391.

8. Major prognostic factors of patients with adult T-cell leukemia-lymphoma: a cooperative study. Lymphoma Study Group (1984-1987). Leuk Res 1991;15:81-90. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2016910.

9. Tsukasaki K, Imaizumi Y, Tawara M, et al. Diversity of leukaemic cell morphology in ATL correlates with prognostic factors, aberrant immunophenotype and defective HTLV-1 genotype. Br J Haematol 1999;105:369-375. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10233406.

10. Tsukasaki K, Hermine O, Bazarbachi A, et al. Definition, prognostic factors, treatment, and response criteria of adult T-cell leukemia-lymphoma: a proposal from an international consensus meeting. J Clin Oncol 2009;27:453-459. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19064971.

11. Tsukasaki K, Tsushima H, Yamamura M, et al. Integration patterns of HTLV-I provirus in relation to the clinical course of ATL: frequent clonal change at crisis from indolent disease. Blood 1997;89:948-956. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9028326.

12. Takasaki Y, Iwanaga M, Tsukasaki K, et al. Impact of visceral involvements and blood cell count abnormalities on survival in adult T-cell leukemia/lymphoma (ATLL). Leuk Res 2007;31:751-757. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17188352.

13. Utsunomiya A, Hanada S, Terada A, et al. Adult T-cell leukemia with leukemia cell infiltration into the gastrointestinal tract. Cancer 1988;61:824-828. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3257406.

14. Teshima T, Akashi K, Shibuya T, et al. Central nervous system involvement in adult T-cell leukemia/lymphoma. Cancer 1990;65:327-332. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2295055.

15. Cheson BD, Bennett JM, Grever M, et al. National Cancer Institute-sponsored Working Group guidelines for chronic lymphocytic leukemia:

revised guidelines for diagnosis and treatment. Blood 1996;87:4990-4997. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8652811.

16. Cheson BD, Horning SJ, Coiffier B, et al. Report of an International Workshop to standardize response criteria for Non-Hodgkin's Lymphomas. J Clin Oncol 1999;17:1244-1253. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10561185.

17. Bazarbachi A, Hermine O. Treatment with a combination of zidovudine and alpha-interferon in naive and pretreated adult T-cell leukemia/lymphoma patients. J Acquir Immune Defic Syndr Hum Retrovirol 1996;13 Suppl 1:186-190. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8797722.

18. Gill PS, Harrington W, Kaplan MH, et al. Treatment of adult T-cell leukemia-lymphoma with a combination of interferon alfa and zidovudine. N Engl J Med 1995;332:1744-1748. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7760890.

19. Hermine O, Allard I, Levy V, et al. A prospective phase II clinical trial with the use of zidovudine and interferon-alpha in the acute and lymphoma forms of adult T-cell leukemia/lymphoma. Hematol J 2002;3:276-282. Available at: http://www.ncbi.nlm.nih.gov/PubMed/12522449.

20. Hermine O, Bouscary D, Gessain A, et al. Brief report: treatment of adult T-cell leukemia-lymphoma with zidovudine and interferon alfa. N Engl J Med 1995;332:1749-1751. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7760891.

21. Matutes E, Taylor GP, Cavenagh J, et al. Interferon alpha and zidovudine therapy in adult T-cell leukaemia lymphoma: response and outcome in 15 patients. Br J Haematol 2001;113:779-784. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11380470.

22. White JD, Wharfe G, Stewart DM, et al. The combination of zidovudine and interferon alpha-2B in the treatment of adult T-cell

leukemia/lymphoma. Leuk Lymphoma 2001;40:287-294. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11426550.

23. Bazarbachi A, Plumelle Y, Carlos Ramos J, et al. Meta-analysis on the use of Zidovudine and interferon-alfa in adult T-cell leukemia/lymphoma showing improved survival in the leukemic subtypes. J Clin Oncol 2010;28:4177-4183. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20585095.

24. Hodson A, Crichton S, Montoto S, et al. Use of Zidovudine and Interferon Alfa With Chemotherapy Improves Survival in Both Acute and Lymphoma Subtypes of Adult T-Cell Leukemia/Lymphoma. J Clin Oncol 2011;29:4696-4701. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22042945.

25. Tsukasaki K, Utsunomiya A, Fukuda H, et al. VCAP-AMP-VECP compared with biweekly CHOP for adult T-cell leukemia-lymphoma: Japan Clinical Oncology Group Study JCOG9801. J Clin Oncol 2007;25:5458-5464. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17968021.

26. Besson C, Panelatti G, Delaunay C, et al. Treatment of adult T-cell leukemia-lymphoma by CHOP followed by therapy with antinucleosides, alpha interferon and oral etoposide. Leuk Lymphoma 2002;43:2275-2279. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12613513.

27. Shapira I, Feldman J, Solomon W. CHOP chemotherapy is better than non-doxorubicin based therapy in patients with HTLV-1 adult T-cell leukemia-lymphoma (ATLL) [abstract]. J Clin Oncol 2005;23:Abstract 6681. Available at: http://meeting.ascopubs.org/cgi/content/abstract/23/16_suppl/6681.

28. Taguchi H, Kinoshita KI, Takatsuki K, et al. An intensive chemotherapy of adult T-cell leukemia/lymphoma: CHOP followed by etoposide, vindesine, ranimustine, and mitoxantrone with granulocyte colony-stimulating factor support. J Acquir Immune Defic Syndr Hum Retrovirol 1996;12:182-186. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8680890.

29. Ratner L, Harrington W, Feng X, et al. Human T-cell leukemia virus reactivation with progression of adult T-cell leukemia-lymphoma. PLoS ONE 2009;4:e4420. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19204798.

30. Yamada Y, Tomonaga M, Fukuda H, et al. A new G-CSF-supported combination chemotherapy, LSG15, for adult T-cell leukaemia-lymphoma: Japan Clinical Oncology Group Study 9303. Br J Haematol 2001;113:375-382. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11380402.

31. Alduaij A, Butera JN, Treaba D, Castillo J. Complete remission in two cases of adult T-cell leukemia/lymphoma treated with hyper-CVAD: a case report and review of the literature. Clin Lymphoma Myeloma Leuk 2010;10:480-483. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21156467.

32. Choi I, Tanosaki R, Uike N, et al. Long-term outcomes after hematopoietic SCT for adult T-cell leukemia/lymphoma: results of prospective trials. Bone Marrow Transplant 2010;46:116-118. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20400987.

33. Fukushima T, Miyazaki Y, Honda S, et al. Allogeneic hematopoietic stem cell transplantation provides sustained long-term survival for patients with adult T-cell leukemia/lymphoma. Leukemia 2005;19:829-834. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15744352.

34. Hishizawa M, Kanda J, Utsunomiya A, et al. Transplantation of allogeneic hematopoietic stem cells for adult T-cell leukemia: a nationwide retrospective study. Blood 2010;116:1369-1376. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20479287.

35. Kami M, Hamaki T, Miyakoshi S, et al. Allogeneic haematopoietic stem cell transplantation for the treatment of adult T-cell leukaemia/lymphoma. Br J Haematol 2003;120:304-309. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12542491.

36. Okamura J, Uike N, Utsunomiya A, Tanosaki R. Allogeneic stem cell transplantation for adult T-cell leukemia/lymphoma. Int J Hematol 2007;86:118-125. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17875524.

37. Utsunomiya A, Miyazaki Y, Takatsuka Y, et al. Improved outcome of adult T cell leukemia/lymphoma with allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 2001;27:15-20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11244433.

38. Shiratori S, Yasumoto A, Tanaka J, et al. A retrospective analysis of allogeneic hematopoietic stem cell transplantation for adult T cell leukemia/lymphoma (ATL): clinical impact of graft-versus-leukemia/lymphoma effect. Biol Blood Marrow Transplant 2008;14:817-823. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18541202.

39. Yonekura K, Utsunomiya A, Takatsuka Y, et al. Graft-versus-adult T-cell leukemia/lymphoma effect following allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 2008;41:1029-1035. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18332910.

40. Ishida T, Hishizawa M, Kato K, et al. Allogeneic hematopoietic stem cell transplantation for adult T-cell leukemia-lymphoma with special emphasis on preconditioning regimen: a nationwide retrospective study. Blood 2012;120:1734-1741. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22689862.

41. Itonaga H, Tsushima H, Taguchi J, et al. Treatment of relapsed adult T-cell leukemia/lymphoma after allogeneic hematopoietic stem cell transplantation: the Nagasaki Transplant Group experience. Blood 2013;121:219-225. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23100309.

42. Ishida T, Joh T, Uike N, et al. Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma: a multicenter phase II study. J Clin Oncol 2012;30:837-842. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22312108.

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43. Yamamoto K, Utsunomiya A, Tobinai K, et al. Phase I study of KW-0761, a defucosylated humanized anti-CCR4 antibody, in relapsed patients with adult T-cell leukemia-lymphoma and peripheral T-cell lymphoma. J Clin Oncol 2010;28:1591-1598. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20177026.

Discussion update in progress

Extranodal NK/T-Cell Lymphomas, Nasal Type

Mature NK/T-cell lymphomas are a rare and distinct subtype of NHL. NK/T-cell lymphomas are predominantly extranodal and majority of these are of nasal type. Among the confirmed cases of T-cell or NK-cell lymphomas (N=1,153) from the International T-cell Lymphoma Project, extranodal NK/T-cell lymphomas (ENKL) were identified in 12% of patients (nasal 68%, extranasal 26%, aggressive or unclassifiable 6%).[1] The frequency was higher in Asia than in Western countries (22% vs. 5%). In the U.S., the data from the Surveillance Epidemiology and End Results (SEER) registry database reported an increase in the incidence of ENKL, nasal type, from 1992 through 2005, with an annual percentage change of 11%.[2] The incidences were also found to be higher in men and in people of Asian and Pacific Island descent. According to outcomes from the International T-Cell Lymphoma Project, the 5-year overall survival (OS) rate for all patients with ENKL was 32%, and the median OS was about 8 months.[1,3]

In the 2008 WHO classification, mature NK-cell neoplasms are classified into 2 subtypes: ENKL, nasal type and aggressive NK-cell leukemia.[4] However, ENKL can have an extranasal presentation.[1,5,6] ENKL, nasal type is often localized to the upper aerodigestive tract including the nasal cavity, nasopharynx, paranasal sinuses, tonsils, hypopharynx, and larynx.[6,7] The most common sites of extranasal involvement or metastatic disease include the skin, testis, and gastrointestinal tract. The most common clinical features of ENKL include nasal obstruction or nasal bleeding due to a mass lesion.[6,7] Compared with patients with nasal type, a greater proportion of the patients with extranasal disease present with advanced stage disease (68% vs. 27%), mass >5 cm (68% vs. 12%), greater than 2 extranodal sites (55% vs. 16%), elevated LDH levels (60% vs. 45%) and B symptoms (54% vs. 39%).[1] The prognosis of ENKL, nasal type is also

better, and was associated with higher 5-year OS rate (42% vs. 9%) and longer median OS (19 months vs. 4 months).[1,3]

Diagnosis

Histopathological features in most cases of ENKL are characterized by diffuse lymphomatous infiltrates, angiocentricity, angiodestructive growth patterns resulting in tissue ischemia and necrosis, and ulceration of mucosal sites.[6] Lymphoma cells can be variable, but are usually medium sized or a mixture of small and large cells. Necrosis is very common in diagnostic biopsies and may delay diagnosis. Biopsy specimen should include edges of the lesions, to increase the odds of having a viable tissue. It may also be useful to perform multiple nasopharyngeal biopsies even in areas that are not clearly involved.

Histopathology and adequate immunophenotyping are essential to confirm the diagnosis. EBV infection is always present in the case of ENKL, and should be determined by EBV-encoded RNA in situ hybridization (EBER-ISH). For high clinical suspicion of ENKL, the initial immunohistochemistry (IHC) panel should include cytoplasmic CD3ε (cCD3ε), CD56 and EBER-ISH. A negative EBER-ISH result should prompt hematopathology review for an alternative diagnosis. Additional recommended markers for the IHC panel include CD20, CD2, CD4, CD5, CD7, CD8, for T-cell lineage. Under certain circumstances, molecular analysis for *TCR* gene rearrangements may be useful; clonal *TCR* rearrangements have been found in about a third of cases with ENKL, nasal type.[1]

The typical immunophenotype for NK-cell ENKL is CD20-, CD2+, cCD3ε+ (surface CD3-), CD4-, CD5-, CD7-/+, CD8-/+, CD43+, CD45RO+, CD56+, TCRαβ-, TCRδγ-, EBV-EBER+, and cytotoxic granule proteins positive (e.g., TIA-1+, granzyme B+).[1,8] For NK-cell lineage, *TCR* and immunoglobulin gene represent germline sequences.

The typical immunophenotype for T-cell lineage is CD2+, cCD3ε+, surface CD3+, variable CD4/CD5/CD7/CD8, TCRαβ+ or TCRδγ+, EBV-EBER+, and cytotoxic granule proteins positive. For T-cell lineage, clonal rearrangements of TCR genes are observed. Ki-67 expression has been reported to be prognostic in patients with stage I/II ENKL, nasal type.[9,10] High Ki-67 expression (65% or more) was associated with a shorter OS and disease-free survival (DFS). In multivariate analysis, Ki-67 expression and primary site of involvement were found to be independent prognostic factors for both OS and DFS.[9]

Workup

The initial workup for ENKL should include a physical examination with complete ENT evaluation of nasopharynx involvement (including Waldeyer's ring), evaluation of testicles and skin. A complete blood count with differential and platelets, comprehensive metabolic panel, measurement of serum uric acid, and lactate dehydrogenase (LDH) levels should be conducted. PET-CT scan and CT scans of chest, abdomen, and pelvis, with contrast of diagnostic quality should be performed. If involved, a dedicated CT scan or MRI of the nasal cavity, hard palate, anterior fossa, and nasopharynx is also essential for initial workup. A MUGA scan or echocardiogram should be performed if treatment with anthracycline or anthracenedione is being considered. Evaluation of bone marrow biopsy and aspirate is recommended. Bone marrow involvement is uncommon at diagnosis and occurs in less than 10% of patients.[11] Morphologically negative biopsies should be evaluated by EBER-ISH, and if positive, should be considered involved.[11-14] Measurement of EBV-DNA viral load is useful in the diagnosis and possibly in the monitoring of the disease. EBV DNA viral load correlates well with clinical stage, response to therapy and poor survival.[15,16] EBV DNA 6.1×10^7 copies/mL or more at presentation has been shown to be associated with an inferior disease-free survival.[15]

The International Prognostic Index (IPI) is most commonly used for patients with aggressive lymphomas. However, the use of IPI in patients with ENKL is limited because most patients present with localized disease, rare involvement of bone marrow and the presence of constitutional symptoms even with localized disease. Recently, Lee et al have proposed a prognostic model specifically for patients with ENKL, nasal type, based on a large, retrospective, multicenter study that included 262 patients.[17] Most patients had received anthracycline-based chemotherapy regimens with or without radiotherapy (RT). This model identified 4 risk groups with different survival outcomes based on the presence or absence of 4 prognostic factors (B symptoms, stage of the disease, LDH levels and regional lymph node involvement). Most patients had received anthracycline-based chemotherapy regimens with or without radiotherapy (RT). The 5-year OS rates were 81% and 64%, respectively, for patients with no risk factors (Group 1-low risk) and one risk factor (Group 2-low-intermediate risk).[17] The corresponding survival rates were 34% and 7%, respectively, for patients with 2 risk factors (Group 3-intermediate high risk) and 3 or 4 risk factors (Group 4-high risk).[17] Local tumor invasion, defined as bony invasion and/or perforation or invasion of the skin, has also been associated with a low probability of complete response (CR), reduced disease-free survival (DFS) and a high frequency (65%) of systemic failure in patients with stage I/II disease.[18]

The NCCN Guidelines panel recommends measurement of EBV DNA load and calculation of NK/T-cell prognostic index as part of initial work up.

Treatment Options

RT is an important component of initial treatment and RT alone has been effective in achieving favorable CR rates compared to

chemotherapy alone in patients with localized ENKL.[19-27] RT doses of 54 Gy or more are associated with favorable OS and DFS outcomes; the 5-year OS and DFS rates were 75.5% and 60% respectively, compared with 46% and 33%, respectively, for patients receiving RT doses of less than 54 Gy.[26] The benefit of RT was noted in the analysis of the aforementioned International T-cell lymphoma Project, which retrospectively reviewed the clinical outcome of patients with ENKL (N=136).[1] More patients with ENKL, nasal type, received RT with or without chemotherapy compared with patients with extranasal ENKL (52% vs. 24%); the remainder of treated patients received chemotherapy alone. In the subgroup of patients with early-stage ENKL, nasal type (n=57), the addition of RT to chemotherapy resulted in significantly improved 3-year OS rate compared with chemotherapy alone (57% vs. 30%).[1] In a retrospective review of patients with localized stage I/II ENKL, nasal type (N=105), RT alone resulted in higher CR rates compared with chemotherapy alone (83% vs. 20%); CR rates improved to 81% among patients who received RT following chemotherapy.[25] The 5-year OS rates were similar among the patient groups that received RT alone (66%; n=31), RT followed by chemotherapy (77%; n=34) and chemotherapy followed by RT (74%; n=37). Notably, the addition of chemotherapy to RT did not appear to improve OS outcomes in this patient population.[25] A recent multicenter retrospective study reported that in patients with ENKL, nasal type (N=36), the use of RT with chemotherapy (either concurrent or sequential) was associated with significantly increased CR rate (90% vs. 33%; *P*<0.0001) and higher 5-year OS (75% vs. 35%: *P*=0.041) compared with chemotherapy alone.[27]

Several studies suggest that concurrent chemoradiation is a feasible and effective treatment for the management of localized ENKL.[28,29] In the phase I/II study conducted by the Japanese Clinical Oncology Group (JCOG0211 study), high risk patients with stage I/II nasal disease (N=33; with lymph node involvement, B symptoms and elevated LDH) were treated with concurrent RT (50 Gy) and 3 courses of chemotherapy with dexamethasone, etoposide, ifosfamide, and carboplatin (DeVIC).[29] With a median follow-up of 32 months, the 2-year OS was 78% and the CR rate was 77%. Long-term follow up from this study (median follow up 68 months) reported 5-year PFS and OS rates of 67% and 73%, respectively.[30] Late toxicities were manageable with few grade 3 or 4 events, which included only one grade 3 event (irregular menstruation) and one grade 4 event (perforation of nasal skin). Similar promising results were reported by a Korean group in a phase II study evaluating concurrent chemoradiotherapy with cisplatin and RT (40–52.8 Gy) followed by three cycles of etoposide, ifosfamide, cisplatin, and dexamethasone (VIPD) in patients with stage I/II nasal ENKL (N=30).[28] Nine of the patients were considered to have higher risk based on the NK/T-cell prognostic index (discussed earlier). The CR rate was 73% after initial chemoradiation and increased to 80% after VIPD chemotherapy. The estimated 3-year PFS and OS rates were 85% and 86%, respectively.[28] Results from these studies support the use of concurrent chemoradiotherapy for patients with stage I/II disease, particularly those patients with high-risk disease features. Concurrent chemoradiation therapy is also the primary treatment option for patients with advanced stage disease as local RT is an essential adjunct for local disease control.

ENKL lymphoma cells are associated with a high expression of P-glycoprotein leading to multidrug resistance that is likely responsible for the poor response to conventional anthracycline based chemotherapy used in other lymphomas.[31] Several studies have confirmed the activity of L-asparaginase-based regimens for patients with advanced, relapsed or refractory disease.[32-36] In a series of

patients with refractory and relapsed ENKL, nasal type (N=45) treated with L-asparaginase-based chemotherapy followed by involved-field RT (IFRT), the overall response rate (ORR) was 82% (CR in 55%). Both 3-year and 5-year OS rates were 67%.[34] The activity of L-asparaginase in combination with methotrexate and dexamethasone (AspaMetDex regimen) was evaluated in a phase II intergroup study in patients with refractory or relapsed ENKL (N=19).[32] After 3 cycles, patients with localized disease were treated with consolidative RT, if not received previously; those with disseminated disease received high-dose therapy with peripheral blood stem cell infusion. The ORR and CR rate after 3 cycles of treatment was 78% and 61%, respectively. The median progression-free survival (PFS) and OS was both 1 year; the absence of anti asparaginase antibodies and the disappearance of serum EBV-DNA were significantly associated with a better outcome.[32]

More recently, a phase II study from the NK-cell Tumor Study Group evaluated the safety and efficacy of a new L-asparaginase-based combination chemotherapy regimen named SMILE (steroid = dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide) in patients with newly diagnosed stage IV, and relapsed or refractory ENKL, nasal type (N=38 evaluable; newly diagnosed, n=20). A total of 28 patients (74%) completed the planned treatment in the phase II study, with an ORR and CR rate of 79% and 45%, respectively.[35] The response rates were not different between previously untreated patients and patients with relapsed disease. The 1-year PFS and OS rates were 53% and 55%, respectively.[35] In a separate analysis from this study, EBV-DNA copy number was also shown to be predictive for response after SMILE chemotherapy; the ORR was 88% in patients with less than 10^5 copies/mL EBV-DNA in whole blood, compared with 44% in patients with >10^5 copies/mL.[37] In addition, the incidence of grade 4 non-hematologic toxicity was

significantly higher among patients with >10^4 copies/mL of EBV-DNA in plasma (55% vs. 14%).[37] A recent phase II study from the Asia Lymphoma Study Group evaluated the SMILE regimen in patients with newly diagnosed or relapsed/refractory NKTL (N=87; relapsed/refractory, n=44; nasal type, n=60).[38] The ORR was 81% (CR in 66%), with similar response rates between newly diagnosed and relapsed/refractory patients. At a median follow up of 31 months, the 4-year DFS was 64% and the 5-year OS was 50%.[38] These data suggest that L-asparaginase-based regimens represent a reasonable option for patients with advanced, relapsed or refractory disease. Long-term benefit needs to be confirmed in larger randomized clinical trials.

Other recent studies have also evaluated the efficacy and safety of L-asparaginase-based regimens following by RT in previously untreated patients with NKTL, nasal type. In a phase II study that evaluated a regimen with 2 or 3 cycles of LVP (L-asparaginase, vincristine and prednisone) combined with RT in newly diagnosed patients with NKTL (N=26), the ORR was 88.5% (CR in 81%); at a median follow up of 27 months, the 2-year PFS and OS rates were 81% and 88.5%, respectively.[39] Grade 3 leukocytopenia occurred in 2 patients (8%), and no grade 4 toxicities or treatment-related deaths were reported.[39] In another phase II study, a regimen with GELOX (gemcitabine, oxaliplatin, and L-asparaginase) followed by IFRT was evaluated in newly diagnosed patients with stage IE/IIE NKTL (N=27).[40] The ORR with this regimen was 96% (CR in 74%), and the 2-year PFS and OS rates were both 86%. Grade 3 or 4 toxicities were infrequent, and no treatment-related deaths were reported.[40] Outcomes from these studies will need to be confirmed in larger prospective studies.

High-dose therapy with autologous stem cell rescue (HDT/ASCR) has been evaluated as a consolidation therapy for patients with early and advanced-stage disease responding to primary therapy. In retrospective

analyses, disease status at the time of HDT/ASCR was the most important prognostic factor for survival and relapse-free survival.[41-43] A retrospective analysis in patients who underwent HDT/ASCR (N=47) showed that among patients with CR at the time of HDT/ASCR, 5-year disease-specific survival rates were significantly higher in the transplant group compared with the historical non-transplant control group (87% and 68% respectively).[43] When stratified by risk based on NK/T-cell prognostic index, there was no significant difference in disease-specific survival rates between the transplant and control groups for patients with low risk (87% vs. 69%), whereas among patients in the high-risk group, the survival benefit with transplant was significantly greater (100% vs. 52%).[43] In a retrospective study by the NK-cell Tumor Study Group, a subgroup of patients with ENKL, nasal type, underwent HDT/ASCR (n=15).[44] Among these patients, 7 were alive in CR at a median 48+ months after transplant (range, 25+ to 87+ months); 6 patients died due to the disease, all within 5 months from transplant (range, 0.2 to 5 months). Most of the patients who were alive in CR had a first or second CR at the time of the transplant.[44] In a recent retrospective analysis from the Lymphoma Working Group of the Japan Society for Hematopoietic Cell Transplantation (JSHCT), outcomes were compared between treatment with autologous (n=60) versus allogeneic (n=74) hematopoietic stem cell transplantation (HSCT) in patients with ENKL.[45] A greater proportion of patients had stage IV disease in the allogeneic compared with the autologous HSCT group (64% vs. 33%), and a smaller proportion in the allogeneic HSCT group had low-risk IPI scores (34% vs. 62%). Thus, patients who underwent autologous HSCT in this series appeared to have better prognostic features. The 2-year OS rate was significantly higher with autologous compared with allogeneic HSCT (69% vs. 41%). However, the type of transplant was not a significant prognostic factor in multivariate

analysis, and when controlling for other factors that were significant (i.e., stage IV disease, non-CR and performance status at transplant).[45]

Allogeneic HSCT has also been evaluated in the management of ENKL in several retrospective patient series and case reports.[44,46-49] In a retrospective, questionnaire-based study of patients with NK-cell malignancies (N=28; ENKL, n=22), chemosensitive and refractory patients underwent allogeneic HSCT with primarily myeloablative regimens.[48] The 2-year PFS and OS rates in this series were 34% and 40%, respectively. Several small case reports have suggested favorable long-term outcomes for patients with relapsed/refractory ENKL who received allogeneic HSCT, with patients achieving continuous remission for 3 to 5 years.[47,49] In a retrospective study by the NK-cell Tumor Study Group, a small subgroup of patients with ENKL, nasal type, underwent allogeneic HSCT (n=5).[44] Two patients were alive in CR at 56+ months and 78+ months after transplant; 1 patient died due to the disease 2 months from transplant, and 2 patients died in CR.[44]

NCCN Recommendations

Because ENKL are rare malignancies, randomized trials comparing different regimens have not been conducted to date. Therefore, standard therapy has not yet been established for patients with ENKL. Most of the available data are from retrospective analyses and small prospective series. It is recommended that patients with ENKL are treated at centers with expertise in the management of this disease and when possible, enrolled on clinical trials.

Induction Therapy

In the NCCN Guidelines, patients with ENKL are stratified by nasal versus extranasal disease at presentation and then by the stage of the disease.[50] Patients with stage I disease are further stratified based on risk factors (age ≥60 years, presence of B symptoms, ECOG

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performance status ≥ 2 or more, regional lymph node involvement, local tumor invasion elevated LDH, histological evidence of high Ki-67 staining and EBV DNA ≥6.1 x 10^7 copies/mL).

Participation in a clinical trial is the preferred option for all patients with ENKL with any stage disease. Selected patients with stage I nasal disease without risk factors can be treated with RT (≥50 Gy) alone. Alternatively, patients with stage I nasal ENKL can be treated similarly to patients with stage I disease with risk factors or to those with stage II disease, with concurrent chemoradiation therapy [RT (50 Gy) and 3 courses of DeVIC or RT (40–52.8 Gy) and cisplatin followed by 3 cycles of VIPD] or sequential chemoradiation [SMILE followed by RT (45–50.4 Gy) or VIPD followed by RT (45–50.4 Gy)]. Patients with stage IV nasal ENKL and patients with extranasal disease (any stage) can be treated with L-asparaginase-based combination chemotherapy (AspaMetDex or SMILE regimen) with or without RT, or concurrent chemoradiation therapy [RT (50 Gy) and 3 courses of DeVIC or concurrent RT(40-52.8 Gy) and cisplatin followed by 3 cycles of VIPD]. Note that pegaspargase should be used in place of L-asparaginase, as the latter is no longer commercially available in the U.S.

Response Assessment and Additional Therapy
Patients are restaged after induction therapy. Restaging should include appropriate imaging studies (CT, MRI or PET-CT) based on the type of study performed at the initial work up, endoscopy with visual inspection, repeat biopsies and measurement of EBV DNA. It should be noted, however, that the role of PET scan is not well established in this disease.

Patients with stage I nasal disease achieving a CR to induction therapy may be observed without further treatment. A CR in this case should also include a negative ENT evaluation. For patients with a PR after

induction, HSCT is a reasonable option; if a donor is available, an allogeneic HSCT is the preferred option. If eligible, HSCT should also be considered for all patients with stage II or IV nasal disease and extranasal disease (any stage) achieving a CR or PR to induction therapy.

For patients with refractory ENKL (nasal or extranasal, and regardless of disease stage), L-asparaginase-based combination chemotherapy (using pegaspargase in place of L-asparaginase), as described for induction therapy, may offer benefit. Only limited data exist regarding the role of HSCT in this patient population. Salvage chemotherapy (with L-asparaginase-based combination therapy, using pegaspargase) or best supportive care is the recommended option for all patients with refractory disease.

References

1. Au W-y, Weisenburger DD, Intragumtornchai T, et al. Clinical differences between nasal and extranasal natural killer/T-cell lymphoma: a study of 136 cases from the International Peripheral T-Cell Lymphoma Project. Blood 2009;113:3931-3937. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19029440.

2. Abouyabis AN, Shenoy PJ, Lechowicz MJ, Flowers CR. Incidence and outcomes of the peripheral T-cell lymphoma subtypes in the United States. Leuk Lymphoma 2008;49:2099-2107. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19021052.

3. Vose J, Armitage J, Weisenburger D. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol 2008;26:4124-4130. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18626005.

4. Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008.

5. Chan JK, Sin VC, Wong KF, et al. Nonnasal lymphoma expressing the natural killer cell marker CD56: a clinicopathologic study of 49 cases of an uncommon aggressive neoplasm. Blood 1997;89:4501-4513. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9192774.

6. Chan JKC, Quintanilla-Martinez L, Ferry JA, Peh S-C. Extranodal NK/T-cell lymphoma, nasal type. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:285-288.

7. Liang R. Advances in the management and monitoring of extranodal NK/T-cell lymphoma, nasal type. Br J Haematol 2009;147:13-21. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19604234.

8. Kwong YL. Natural killer-cell malignancies: diagnosis and treatment. Leukemia 2005;19:2186-2194. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16179910.

9. Kim SJ, Kim BS, Choi CW, et al. Ki-67 expression is predictive of prognosis in patients with stage I/II extranodal NK/T-cell lymphoma, nasal type. Ann Oncol 2007;18:1382-1387. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17693651.

10. Yasuda H, Sugimoto K, Imai H, et al. Expression levels of apoptosis-related proteins and Ki-67 in nasal NK / T-cell lymphoma. Eur J Haematol 2009;82:39-45. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18778369.

11. Wong KF, Chan JK, Cheung MM, So JC. Bone marrow involvement by nasal NK cell lymphoma at diagnosis is uncommon. Am J Clin Pathol 2001;115:266-270. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11211616.

12. Chim CS, Ma ESK, Loong F, Kwong YL. Diagnostic cues for natural killer cell lymphoma: primary nodal presentation and the role of in situ hybridisation for Epstein-Barr virus encoded early small RNA in detecting occult bone marrow involvement. J Clin Pathol 2005;58:443-445. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15790718.

13. Huang W-T, Chang K-C, Huang G-C, et al. Bone marrow that is positive for Epstein-Barr virus encoded RNA-1 by in situ hybridization is related with a poor prognosis in patients with extranodal natural killer/T-cell lymphoma, nasal type. Haematologica 2005;90:1063-1069. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16079105.

14. Lee J, Suh C, Huh J, et al. Effect of positive bone marrow EBV in situ hybridization in staging and survival of localized extranodal natural killer/T-cell lymphoma, nasal-type. Clin Cancer Res 2007;13:3250-3254. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17545530.

15. Au W-Y, Pang A, Choy C, et al. Quantification of circulating Epstein-Barr virus (EBV) DNA in the diagnosis and monitoring of natural killer cell and EBV-positive lymphomas in immunocompetent patients. Blood 2004;104:243-249. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15031209.

16. Kim HS, Kim KH, Kim KH, et al. Whole blood Epstein-Barr virus DNA load as a diagnostic and prognostic surrogate: extranodal natural killer/T-cell lymphoma. Leuk Lymphoma 2009;50:757-763. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19330658.

17. Lee J, Suh C, Park YH, et al. Extranodal natural killer T-cell lymphoma, nasal-type: a prognostic model from a retrospective multicenter study. J Clin Oncol 2006;24:612-618. Available at: http://www.ncbi.nlm.nih.gov/PubMed/16380410.

18. Kim TM, Park YH, Lee SY, et al. Local tumor invasiveness is more predictive of survival than International Prognostic Index in stage I(E)/II(E) extranodal NK/T-cell lymphoma, nasal type. Blood 2005;106:3785-3790. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16109779.

19. Kim GE, Lee SW, Chang SK, et al. Combined chemotherapy and radiation versus radiation alone in the management of localized angiocentric lymphoma of the head and neck. Radiother Oncol 2001;61:261-269. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11730995.

20. Cheung MMC, Chan JKC, Lau W-h, et al. Early stage nasal NK/T-cell lymphoma: clinical outcome, prognostic factors, and the effect of treatment modality. Int J Radiat Oncol Biol Phys 2002;54:182-190. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12182990.

21. Chim CS, Ma SY, Au WY, et al. Primary nasal natural killer cell lymphoma: long-term treatment outcome and relationship with the International Prognostic Index. Blood 2004;103:216-221. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12933580.

22. Li CC, Tien HF, Tang JL, et al. Treatment outcome and pattern of failure in 77 patients with sinonasal natural killer/T-cell or T-cell lymphoma. Cancer 2004;100:366-375. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14716773.

23. You JY, Chi KH, Yang MH, et al. Radiation therapy versus chemotherapy as initial treatment for localized nasal natural killer (NK)/T-cell lymphoma: a single institute survey in Taiwan. Ann Oncol 2004;15:618-625. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15033670.

24. Kim K, Chie EK, Kim CW, et al. Treatment outcome of angiocentric T-cell and NK/T-cell lymphoma, nasal type: radiotherapy versus chemoradiotherapy. Jpn J Clin Oncol 2005;35:1-5. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15681596.

25. Li Y-X, Yao B, Jin J, et al. Radiotherapy as primary treatment for stage IE and IIE nasal natural killer/T-cell lymphoma. J Clin Oncol 2006;24:181-189. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16382127.

26. Huang MJ, Jiang Y, Liu WP, et al. Early or up-front radiotherapy improved survival of localized extranodal NK/T-cell lymphoma, nasal-type in the upper aerodigestive tract. Int J Radiat Oncol Biol Phys 2008;70:166-174. Available at: http://www.ncbi.nlm.nih.gov/PubMed/17919841.

27. Chauchet A, Michallet AS, Berger F, et al. Complete remission after first-line radio-chemotherapy as predictor of survival in extranodal NK/T cell lymphoma. J Hematol Oncol 2012;5:27. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22682004.

28. Kim SJ, Kim K, Kim BS, et al. Phase II trial of concurrent radiation and weekly cisplatin followed by VIPD chemotherapy in newly diagnosed, stage IE to IIE, nasal, extranodal NK/T-Cell Lymphoma: Consortium for Improving Survival of Lymphoma study. J Clin Oncol 2009;27:6027-6032. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19884539.

29. Yamaguchi M, Tobinai K, Oguchi M, et al. Phase I/II study of concurrent chemoradiotherapy for localized nasal natural killer/T-cell lymphoma: Japan Clinical Oncology Group Study JCOG0211. J Clin

Oncol 2009;27:5594-5600. Available at:
http://www.ncbi.nlm.nih.gov/PubMed/19805668.

30. Yamaguchi M, Tobinai K, Oguchi M, et al. Concurrent chemoradiotherapy for localized nasal natural killer/T-cell lymphoma: an updated analysis of the Japan clinical oncology group study JCOG0211. J Clin Oncol 2012;30:4044-4046. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23045573.

31. Yamaguchi M, Kita K, Miwa H, et al. Frequent expression of P-glycoprotein/MDR1 by nasal T-cell lymphoma cells. Cancer 1995;76:2351-2356. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8635042.

32. Jaccard A, Gachard N, Marin B, et al. Efficacy of L-asparaginase with methotrexate and dexamethasone (AspaMetDex regimen) in patients with refractory or relapsing extranodal NK/T-cell lymphoma, a phase 2 study. Blood 2011;117:1834-1839. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21123825.

33. Jaccard A, Petit B, Girault S, et al. L-asparaginase-based treatment of 15 western patients with extranodal NK/T-cell lymphoma and leukemia and a review of the literature. Ann Oncol 2009;20:110-116. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18701429.

34. Yong W, Zheng W, Zhu J, et al. L-asparaginase in the treatment of refractory and relapsed extranodal NK/T-cell lymphoma, nasal type. Ann Hematol 2009;88:647-652. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19107482.

35. Yamaguchi M, Kwong YL, Kim WS, et al. Phase II Study of SMILE Chemotherapy for Newly Diagnosed Stage IV, Relapsed, or Refractory Extranodal Natural Killer (NK)/T-Cell Lymphoma, Nasal Type: The NK-Cell Tumor Study Group Study. J Clin Oncol 2011;29:4410-4416. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21990393.

36. Yamaguchi M, Suzuki R, Kwong YL, et al. Phase I study of dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) chemotherapy for advanced-stage, relapsed or refractory extranodal natural killer (NK)/T-cell lymphoma and leukemia. Cancer Sci 2008;99:1016-1020. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18294294.

37. Suzuki R, Kimura H, Kwong Y-L, et al. Pretreatment EBV-DNA Copy Number Is Predictive for Response to SMILE Chemotherapy for Newly-Diagnosed Stage IV, Relapsed or Refractory Extranodal NK/T-Cell Lymphoma, Nasal Type: Results of NKTSG Phase II Study [abstract]. Blood 2010;116:Abstract 2873. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/2873.

38. Kwong YL, Kim WS, Lim ST, et al. SMILE for natural killer/T-cell lymphoma: analysis of safety and efficacy from the Asia Lymphoma Study Group. Blood 2012;120:2973-2980. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22919026.

39. Jiang M, Zhang H, Jiang Y, et al. Phase 2 trial of "sandwich" L-asparaginase, vincristine, and prednisone chemotherapy with radiotherapy in newly diagnosed, stage IE to IIE, nasal type, extranodal natural killer/T-cell lymphoma. Cancer 2012;118:3294-3301. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22139825.

40. Wang L, Wang ZH, Chen XQ, et al. First-line combination of gemcitabine, oxaliplatin, and L-asparaginase (GELOX) followed by involved-field radiation therapy for patients with stage IE/IIE extranodal natural killer/T-cell lymphoma. Cancer 2013;119:348-355. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22811078.

41. Au WY, Lie AKW, Liang R, et al. Autologous stem cell transplantation for nasal NK/T-cell lymphoma: a progress report on its value. Ann Oncol 2003;14:1673-1676. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14581277.

42. Kim HJ, Bang SM, Lee J, et al. High-dose chemotherapy with autologous stem cell transplantation in extranodal NK/T-cell lymphoma: a retrospective comparison with non-transplantation cases. Bone

Marrow Transplant 2006;37:819-824. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16547486.

43. Lee J, Au W-Y, Park MJ, et al. Autologous hematopoietic stem cell transplantation in extranodal natural killer/T cell lymphoma: a multinational, multicenter, matched controlled study. Biol Blood Marrow Transplant 2008;14:1356-1364. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19041057.

44. Suzuki R, Suzumiya J, Nakamura S, et al. Hematopoietic stem cell transplantation for natural killer-cell lineage neoplasms. Bone Marrow Transplant 2006;37:425-431. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16400344.

45. Suzuki R, Kako S, Hyo R, et al. Comparison of Autologous and Allogeneic Hematopoietic Stem Cell Transplantation for Extranodal NK/T-Cell Lymphoma, Nasal Type: Analysis of the Japan Society for Hematopoietic Cell Transplantation (JSHCT) Lymphoma Working Group [abstract]. Blood 2011;118:Abstract 503. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/118/21/503.

46. Ennishi D, Maeda Y, Fujii N, et al. Allogeneic hematopoietic stem cell transplantation for advanced extranodal natural killer/T-cell lymphoma, nasal type. Leuk Lymphoma 2011;52:1255-1261. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21599584.

47. Li M, Gao C, Li H, et al. Allogeneic haematopoietic stem cell transplantation as a salvage strategy for relapsed or refractory nasal NK/T-cell lymphoma. Med Oncol 2011;28:840-845. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20414818.

48. Murashige N, Kami M, Kishi Y, et al. Allogeneic haematopoietic stem cell transplantation as a promising treatment for natural killer-cell neoplasms. Br J Haematol 2005;130:561-567. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16098071.

49. Yokoyama H, Yamamoto J, Tohmiya Y, et al. Allogeneic hematopoietic stem cell transplant following chemotherapy containing l-asparaginase as a promising treatment for patients with relapsed or refractory extranodal natural killer/T cell lymphoma, nasal type. Leuk Lymphoma 2010;51:1509-1512. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20496989.

50. Kohrt H, Lee M, Advani R. Risk stratification in extranodal natural killer/T-cell lymphoma. Expert Rev Anticancer Ther 2010;10:1395-1405. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20836675.

T-cell Prolymphocytic Leukemia

Diagnosis

T-cell prolymphocytic leukemia (T-PLL) is a rare malignancy, comprising approximately 2% of all mature lymphoid malignancies.[1] Clinically, patients frequently present with lymphadenopathy, hepatomegaly, splenomegaly, and elevated WBC counts.[1,2] Skin lesions can also be present in about 30% of patients.[2]

Morphological examinations of peripheral blood, as well as adequate immunophenotyping by flow cytometry, are essential to establish the diagnosis of T-PLL. Peripheral blood smears show prolymphocytes with round or oval nuclei in about half of the cases, and irregular nuclei (often with convolutions) in the remaining cases; in most cases (about 75%), the typically morphology comprises medium-sized prolymphocytes with agranular basophilic cytoplasm and a single visible nucleolus, while in about 20% to 25% of cases, the cell is small and the nucleolus may not be readily visible.[1,3] Peripheral blood flow cytometry analysis should include the following markers: TdT, CD1a, CD2, CD3, CD4, CD5, CD7, CD8, CD52, and TCRαβ. Under certain circumstances, immunohistochemistry (IHC) analysis on bone marrow biopsy samples may be useful. In such cases, the IHC panel should include TdT, CD1a, CD2, CD3, CD5, and TCL-1. However, in general, bone marrow biopsy is not essential for establishing a diagnosis of T-PLL. The immunophenotype of T-PLL is consistent with a mature post-thymic T-cell phenotype, with a typical immunophenotype that is TdT-, CD1a-, CD2+, CD5+, and CD7+.[1,3] CD3 expression may be weak on the cell surface but is usually expressed in the cytoplasm. In 65% of cases, the cells are CD4+/CD8- but cases with CD4+/CD8+ (21%) and CD4-/CD8+ (13%) can also be seen.[1,2] CD52 is often highly expressed.[1,4] Diffuse infiltration in the bone marrow is typically observed with T-PLL, but diagnosis is difficult to establish based on bone marrow evaluation alone. Tissue histology is not considered essential to establish the diagnosis. Frequent cytogenetic abnormalities in T-PLL include inversions or translocations involving chromosome 14, most commonly, inv(14)(q11;q32) or t(14;14)(q11;q32), which are associated with the *TCL-1* oncogene.[2,5,6] Although less frequent, the translocation t(X;14)(q28;q11), associated with the *MTCP-1* oncogene, may also occur. Overexpression of *TCL-1* and *MTCP-1* has been implicated in the pathogenesis of T-PLL.[7-9] Abnormalities in chromosome 8, mainly trisomy 8q, are also frequently observed.[2,5,6] Deletions or mutations to the tumor suppressor gene *ATM*, which localizes to the chromosome region 11q22-23, have also been detected in patients with T-PLL.[10,11] This gene is mutated in patients with ataxia telangiectasia, and these patients appear to be predisposed to developing T-cell malignancies, including T-PLL; thus, it is postulated that abnormalities in the *ATM* gene may also be one of the key events in the pathogenesis of T-PLL.[10,11] Cytogenetics by conventional karyotyping and/or FISH to detect chromosome 14 abnormalities and trisomy 8 should be performed at the time of diagnostic workup. Under certain circumstances, molecular genetics to detect *TCR* gene rearrangements, *MTCP-1* gene rearrangements, *ATM* mutations, or *TCL-1* overexpression, may be useful.

Workup

The initial workup for T-PLL should comprise a comprehensive medical history and physical examination, including careful evaluation of lymph nodes, spleen, and liver, in addition to a complete skin examination and evaluation of performance status. Laboratory assessments should include standard blood work including CBC with differential, and a comprehensive metabolic panel, as well as measurements of serum lactate dehydrogenase (LDH). Bone marrow evaluation is generally unnecessary, as evaluation of peripheral blood

smears and immunophenotyping are sufficient to establish the diagnosis of T-PLL, as discussed above; however, bone marrow assessments may be useful in some cases. CT scans of the chest, abdomen and pelvis should also be performed at the time of initial workup. PET-CT scans may also be useful in selected cases. If treatment regimens containing anthracyclines or anthracenediones are being considered, a MUGA scan or echocardiogram may be useful, particularly for older patients or for patients with a prior history of cardiac disease. Serology for detection of antibodies against the human T-lymphotropic leukemia virus type 1 (HTLV-1) may be useful, especially to distinguish adult T-cell leukemia/lymphoma from T-PLL (HTLV-1 should be negative in the latter). If serology shows positivity for HTLV-1 by ELISA, a confirmatory Western blot should be performed. Screening for active infections and cytomegalovirus (CMV) serology should be strongly considered prior to initiation of treatment with alemtuzumab-containing regimens.

Treatment Options

In the minority of cases where patients are asymptomatic and have a more indolent course of disease, observation is a reasonable approach until symptoms develop. In most cases of T-PLL, however, patients are symptomatic at the time of presentation. T-PLL is an aggressive malignancy associated with rapid disease progression. In an early study of patients with T-PLL (N=78) treated with alkylating agents, pentostatin, or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), the median overall survival (OS) was only 7.5 months; among the subgroup of patients who responded to pentostatin (n=15), the median OS was 16 months.[2] In a retrospective analysis of patients (both previously untreated and treated) with post-thymic T-cell malignancies treated with pentostatin, the overall response rate (ORR) was 45% and complete response [CR] 9% in the subgroup of patients

with T-PLL (n=55).[12] The median duration of response was short, however, at 6 months (range, 3–16 months). The median OS from treatment initiation was 17.5 months for responding patients and 9 months for non-responders.[12]

More recently, treatment with the anti-CD52 monoclonal antibody alemtuzumab has shown high response rates in both previously treated and untreated patients with T-PLL.[13-16] In a study that primarily included pretreated patients with T-PLL (N=39; previously treated, n=37), intravenous (IV) alemtuzumab resulted in an ORR of 76% (CR in 60%).[14] The median disease-free interval (from end of therapy to relapse) was 7 months. Among the patients who were pretreated (n=37), none had achieved a CR to previous therapy and 61.5% were resistant to prior treatments.[14] The median OS for all patients was 10 months, and was 16 months for patients with a CR. Following alemtuzumab, 11 patients proceeded to hematopoietic stem cell transplant (HSCT; autologous HSCT, n=7; allogeneic HSCT, n=4).[14] Outcomes were similar in a subsequent report, in which IV alemtuzumab induced an ORR of 74% (CR in 60%) in patients with relapsed/refractory T-PLL (n=45); the 4-year OS rate in this patient group was 18%.[13] In a larger study in patients with T-PLL (N=76; previously treated, n=72), treatment with IV alemtuzumab induced an ORR of 51% (CR in 39.5%); among the 4 patients who received alemtuzumab as first-line therapy, 3 achieved a CR.[15] The median time to progression (TTP) for all patients was 4.5 months, and the median OS was 7.5 months. Among the patients who achieved a CR, the median response duration and OS was 9 months and 15 months, respectively.[15] In a recent study that evaluated alemtuzumab in the first-line setting using the IV route or subcutaneous (SC) delivery in patients with T-PLL, response rates were found to be inferior with the SC route of alemtuzumab.[13] In the small number of patients who were

treated with first-line SC alemtuzumab (n=9), the ORR was 33% with no CRs; moreover, 2 of the patients (22%) died of progression of disease during therapy. In contrast, first-line IV alemtuzumab (n=32) induced an ORR of 91% with CR in 81% of patients. The most common toxicities reported with alemtuzumab in patients with T-PLL included infusion-related reactions, prolonged lymphocytopenia, and infectious events, including opportunistic infections.[14,15]

Alemtuzumab has also been evaluated as part of combination regimens in patients with T-PLL. In a phase II study that evaluated the combination of alemtuzumab and pentostatin in patients with T-cell malignancies, the subgroup of patients with T-PLL (n=13) showed an ORR of 69%, with a CR in 62% of patients.[17] The median PFS and OS for this subgroup of patients were 8 months and 10 months, respectively. The study included both patients with previously treated and untreated disease.[17] In a study conducted by the German CLL Study Group in patients with T-PLL (N=18 evaluable; previously treated, n=6), alemtuzumab was given sequentially (as consolidation therapy) to patients who responded to initial courses of chemotherapy with FCM (fludarabine, cyclophosphamide, mitoxantrone).[18] Patients with stable disease or progression after 2 courses of FCM were also eligible to received alemtuzumab. Following FCM chemotherapy, 15 patients received consolidation with IV alemtuzumab. The ORR after FCM and after alemtuzumab was 66% and 88%, respectively. The median PFS and OS following FCM with alemtuzumab was 11 months and 19 months, respectively.[18] In a recent follow-up report from this study (N=25; previously treated, n=9), the ORR after FCM was 68% with a CR in 24%.[19] After consolidation with alemtuzumab, the ORR increased to 92% with a CR in 48% (intent-to-treat population). The median PFS and OS were 12 months and 17 months, respectively. PFS was shorter among patients with higher TCL-1 expression levels. Among the patients who received consolidation with alemtuzumab

(n=21), CMV reactivation occurred in 13 patients (62%); 9 of these cases were clinical relevant CMV infections (43%).[19] Outcomes with this treatment approach appear promising; however, the high rate of CMV reactivation warrants careful monitoring (and preemptive antiviral therapy upon increasing viral load) to prevent the development of CMV-related complications.

The potential utility of allogeneic hematopoietic stem cell transplant (HSCT) in patients with T-PLL has been reported in a number of individual case studies.[14,20-23] A retrospective study investigated the role of HSCT (allogeneic or autologous) following treatment with alemtuzumab in patients with T-PLL (N=28), and compared the outcomes to a retrospective cohort of patients who received alemtuzumab alone.[24] Among the group of patients who received allogeneic HSCT after alemtuzumab (n=13), all patients achieved a CR following HSCT (except one patient who was not evaluable), and 5 were alive in CR at a median of 28 months (range, 25 to 110 months) follow-up from transplant. Four patients had relapsed (at 5, 9, 24, and 31 months from transplant) and died; in addition, 4 patients died in CR, resulting in a treatment-related mortality (TRM) rate of 31%. The median OS (from start of alemtuzumab therapy) for all patients who underwent allogeneic HSCT was 33 months; this appeared more favorable to the median OS of 20 months among patients who did not receive transplant after alemtuzumab.[24] Retrospective analyses of data from databases have evaluated the role of allogeneic HSCT in T-PLL.[25-27] In a review of data from the CIBMTR database, which included patients with PLL treated with allogeneic HSCT (N=47; T-PLL, n=21 [45%]; B-PLL or unspecified lineage in the remaining cases), the 1-year PFS and OS rates were 33% and 48%, respectively.[25] The median OS for these patients was 11 months. For the subgroup of patients with T-PLL (n=21), the median PFS with allogeneic HSCT was 5 months. The 1-year cumulative incidence of

TRM was 28%; the 1-year incidence of relapse or disease progression was 39%.[25] In another study, outcomes of allogeneic HSCT in patients with T-PLL were evaluated based on data from the EBMT database (N=41).[26] The median PFS and OS were 10 months and 12 months, respectively. The 3-year relapse-free survival (RFS) and OS rates were 19% and 21%, respectively. The 3-year TRM and relapse rates were 41% for both endpoints; most relapses (71% of cases) occurred within the first year following transplant.[26] Patients who underwent HSCT in first remission (CR or partial remission [PR]) tended to have a lower relapse rate (2-year rate: 30% vs. 46%) and higher event-free survival rate (2-year rate: 39% vs. 15%) compared with those transplanted with advanced disease. Based upon multivariate analysis, the use of total body irradiation (TBI) conditioning and a shorter interval between diagnosis and transplant were significant independent predictors of longer RFS with allogeneic HSCT. None of the variables evaluated were independent predictors of OS outcomes.[26] In another recent retrospective study, outcomes of allogeneic HSCT in patients with T-PLL were evaluated based on data from a multicenter French registry (N=20; transplanted in CR, n=9).[27] The majority of these patients (85%) had received alemtuzumab prior to HSCT. The CR rate after allogeneic HSCT was 85%. At a median follow up of 29 months, 10 patients remain alive with 7 patients in CR. TRM occurred in 6 patients (30%), with early TRM in 2 of the patients. Four deaths occurred due to disease progression. The estimated 3-year PFS and OS were 29% and 42%, respectively.[27] The 3-year incidence of TRM was 38%. The incidence of relapse was 51%, with a median time to relapse (post-HSCT) of 14 months.[27] Although the available data are based on retrospective evaluations, allogeneic HSCT may offer the best chance for long-term disease control in a subgroup of patients with T-PLL.

Only limited data have been published on the use of autologous HSCT in patients with T-PLL. In the aforementioned study of alemtuzumab in patients with primarily pretreated T-PLL, a small group of patients (n=7) underwent autologous HSCT after achieving a CR with alemtuzumab therapy.[14] Five of these patients were in first CR at the time of HSCT while 2 patients were in second CR. Among these patients, the median OS from time of transplant was 12 months (range, 5+ to 19 months). Four patients (including the 2 patients transplanted in second CR) relapsed after 5 to 14 months and died due to progressive disease. At the time of the report, 3 patients were alive at 5, 7, and15 months after transplant.[14] In a more recent update, a retrospective analysis evaluated additional patients with T-PLL who underwent autologous HSCT following treatment with alemtuzumab (n=15).[24] All of these patients achieved a CR following HSCT, and 5 were alive in CR at a median of 81 months (range, 8 to 115 months) follow-up from transplant. Nine patients had relapsed at a median of 15 months (range, 5 to 56 months) from transplant, and died; 1 patient died in CR due to an infection and multi-organ failure (TRM of 7%).[24] The median OS (from start of alemtuzumab therapy) for all patients who underwent autologous HSCT was 52 months, which appeared to compare favorably to that of patients who received alemtuzumab alone (20 months). No statistically significant difference in OS was observed between autologous versus allogeneic HSCT (52 months vs. 33 months).[24] At this time, however, the limited availability of data precludes any definitive conclusions regarding the role of autologous HSCT in the management of T-PLL.

NCCN Recommendations

Given the poor prognosis associated with T-PLL, the NCCN Guidelines panel recommends that patients be managed in a clinical trial for novel therapies. In the absence of suitable clinical trials, regimens containing

alemtuzumab are recommended as the initial treatment for patients with symptomatic T-PLL. Based on data showing inferior response rates with the SC route of alemtuzumab,[13,28] the panel recommends that alemtuzumab be administered via IV delivery. Initial treatment options include single-agent therapy with IV alemtuzumab, or alemtuzumab in combination with pentostatin. Sequential therapy with FCM followed by IV alemtuzumab may also be considered. Given the potential risks for viral reactivation and opportunistic infections (e.g., CMV reactivation/infection, *Pneumocystis jiroveci* pneumonia [PCP]) with alemtuzumab therapy, patients should be given antiviral prophylaxis and prophylactic therapy for PCP (e.g., TMP-SMX). In addition, patients should be routinely monitored for CMV reactivation using quantitative PCR test, and treated with preemptive antiviral therapy, as appropriate (see Guidelines section for Supportive Care for NHL).

In patients who achieve a response (CR or partial response [PR]) following initial therapy, consolidation with allogeneic HSCT is recommended if a donor is available, and if the patient is physically fit enough to undergo the transplant procedure. For patients who relapse following an initial response to therapy, or for those who do not respond to therapy (or have progressive disease during therapy), second-line therapy options include clinical trial participation (preferred) or alternate regimens not used during first-line therapy.

References

1. Dearden CE. T-cell prolymphocytic leukemia. Clin Lymphoma Myeloma 2009;9 Suppl 3:S239-243. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19778847.

2. Matutes E, Brito-Babapulle V, Swansbury J, et al. Clinical and laboratory features of 78 cases of T-prolymphocytic leukemia. Blood 1991;78:3269-3274. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1742486.

3. Catovsky D, Muller-Hermelink HK, Ralfkiaer E, eds. T-cell prolymphocytic leukaemia. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO Classification of Tumours or Haematopoietic and Lymphoid Tissues (ed 4th). Lyon2008.

4. Ginaldi L, De Martinis M, Matutes E, et al. Levels of expression of CD52 in normal and leukemic B and T cells: correlation with in vivo therapeutic responses to Campath-1H. Leuk Res 1998;22:185-191. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9593475.

5. Brito-Babapulle V, Catovsky D. Inversions and tandem translocations involving chromosome 14q11 and 14q32 in T-prolymphocytic leukemia and T-cell leukemias in patients with ataxia telangiectasia. Cancer Genet Cytogenet 1991;55:1-9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1913594.

6. Maljaei SH, Brito-Babapulle V, Hiorns LR, Catovsky D. Abnormalities of chromosomes 8, 11, 14, and X in T-prolymphocytic leukemia studied by fluorescence in situ hybridization. Cancer Genet Cytogenet 1998;103:110-116. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9614908.

7. Gritti C, Dastot H, Soulier J, et al. Transgenic mice for MTCP1 develop T-cell prolymphocytic leukemia. Blood 1998;92:368-373. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9657733.

8. Herling M, Patel KA, Teitell MA, et al. High TCL1 expression and intact T-cell receptor signaling define a hyperproliferative subset of T-cell prolymphocytic leukemia. Blood 2008;111:328-337. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17890451.

9. Virgilio L, Lazzeri C, Bichi R, et al. Deregulated expression of TCL1 causes T cell leukemia in mice. Proc Natl Acad Sci U S A 1998;95:3885-3889. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9520462.

10. Stilgenbauer S, Schaffner C, Litterst A, et al. Biallelic mutations in the ATM gene in T-prolymphocytic leukemia. Nat Med 1997;3:1155-1159. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9334731.

11. Stoppa-Lyonnet D, Soulier J, Lauge A, et al. Inactivation of the ATM gene in T-cell prolymphocytic leukemias. Blood 1998;91:3920-3926. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9573030.

12. Mercieca J, Matutes E, Dearden C, et al. The role of pentostatin in the treatment of T-cell malignancies: analysis of response rate in 145 patients according to disease subtype. J Clin Oncol 1994;12:2588-2593. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7989933.

13. Dearden CE, Khot A, Else M, et al. Alemtuzumab therapy in T-cell prolymphocytic leukaemia: comparing efficacy in a series treated intravenously and a study piloting the subcutaneous route. Blood 2011;118:5799-5802. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21948296.

14. Dearden CE, Matutes E, Cazin B, et al. High remission rate in T-cell prolymphocytic leukemia with CAMPATH-1H. Blood 2001;98:1721-1726. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11535503.

15. Keating MJ, Cazin B, Coutre S, et al. Campath-1H treatment of T-cell prolymphocytic leukemia in patients for whom at least one prior chemotherapy regimen has failed. J Clin Oncol 2002;20:205-213. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11773171.

16. Pawson R, Dyer MJ, Barge R, et al. Treatment of T-cell prolymphocytic leukemia with human CD52 antibody. J Clin Oncol

1997;15:2667-2672. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/9215839.

17. Ravandi F, Aribi A, O'Brien S, et al. Phase II study of alemtuzumab in combination with pentostatin in patients with T-cell neoplasms. J Clin Oncol 2009;27:5425-5430. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/19805674.

18. Hopfinger G, Busch R, Barbara E, et al. TPLL-1 Protocol of the German CLL Study Group (GCLLSG) - A Prospective Phase II Trial of Fludarabine Phosphate, Mitoxantrone and Cyclophosphamide (FMC) Followed by Alemtuzumab Consolidation in T-PLL [abstract]. Blood 2007;110:Abstract 2039. Available at:
http://abstracts.hematologylibrary.org/cgi/content/abstract/110/11/2039.

19. Hopfinger G, Busch R, Pflug N, et al. Sequential chemoimmunotherapy of fludarabine, mitoxantrone, and cyclophosphamide induction followed by alemtuzumab consolidation is effective in T-cell prolymphocytic leukemia. Cancer 2013. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/23512246.

20. Collins RH, Pineiro LA, Agura ED, Fay JW. Treatment of T prolymphocytic leukemia with allogeneic bone marrow transplantation. Bone Marrow Transplant 1998;21:627-628. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/9580345.

21. de Lavallade H, Faucher C, Furst S, et al. Allogeneic stem cell transplantation after reduced-intensity conditioning in a patient with T-cell prolymphocytic leukemia: graft-versus-tumor effect and long-term remission. Bone Marrow Transplant 2006;37:709-710. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/16474410.

22. Garderet L, Bittencourt H, Kaliski A, et al. Treatment of T-prolymphocytic leukemia with nonmyeloablative allogeneic stem cell transplantation. Eur J Haematol 2001;66:137-139. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/11168523.

23. Murase K, Matsunaga T, Sato T, et al. Allogeneic bone marrow transplantation in a patient with T-prolymphocytic leukemia with small-intestinal involvement. Int J Clin Oncol 2003;8:391-394. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/14663643.

24. Krishnan B, Else M, Tjonnfjord GE, et al. Stem cell transplantation after alemtuzumab in T-cell prolymphocytic leukaemia results in longer survival than after alemtuzumab alone: a multicentre retrospective study. Br J Haematol 2010;149:907-910. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/20201944.

25. Kalaycio ME, Kukreja M, Woolfrey AE, et al. Allogeneic hematopoietic cell transplant for prolymphocytic leukemia. Biol Blood Marrow Transplant 2010;16:543-547. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/19961946.

26. Wiktor-Jedrzejczak W, Dearden C, de Wreede L, et al. Hematopoietic stem cell transplantation in T-prolymphocytic leukemia: a retrospective study from the European Group for Blood and Marrow Transplantation and the Royal Marsden Consortium. Leukemia 2011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22116553.

27. Guillaume T, Beguin Y, Leblond V, et al. Allogeneic Hematopoietic Stem Cell Transplantation for T-Prolymphocytic leukemia: A Retrospective Analysis From the Societe francaise De Greffe De Moelle Et De Therapie Cellulaire [abstract]. Blood 2012;120:Abstract 2008. Available at:
http://abstracts.hematologylibrary.org/cgi/content/abstract/120/21/2008.

28. Khot AtS, Matutes E, Kaczmarek PA, et al. Alemtuzumab Administered by Subcutaneous Route Is Less Effective Than Intravenous Route for First Line Therapy of T-Cell Prolymphocytic Leukaemia: Results of a Pilot Study (UKCLL05) [abstract]. Blood 2008;112:Abstract 4204. Available at:
http://abstracts.hematologylibrary.org/cgi/content/abstract/112/11/4204.

Post-Transplant Lymphoproliferative Disorders

Post-transplant lymphoproliferative disorders (PTLD) are a heterogeneous group of lymphoid neoplasms associated with immunosuppression following solid organ transplantation (SOT) or allogeneic hematopoietic stem cell transplantation (HSCT).[1-4] PTLD following autologous HSCT is very rare. The majority of PTLD following both allogeneic HSCT and SOT are of B cell origin, and are usually associated with the Epstein Barr virus (EBV).[2,5-8] Although rare, PTLD of T cell or NK cell origin can also occur (EBV-associated in approximately 30% of cases), and tend to occur late (median 6 years post-transplant in one series).[9] EBV-negative PTLD has been shown to be a late serious complication of transplantation, and tend to occur later (>2 years) after SOT than EBV-positive disease.[10-12] Gene expression profiling studies have shown that EBV negative PTLD are biologically distinct from their EBV associated counterparts.[13,14] PTLD following HSCT are usually of donor origin, whereas PTLD following SOT are of recipient origin in the majority of cases, with a minority of donor derived cases that often involve the grafted organ.[2,3,15-20]

The incidence of PTLD following allogeneic HSCT ranges from about 1% to 3% with a slightly higher incidence in patients who are recipients of cord blood transplant.[1,21-24] The large majority of these PTLD occur early, within 6 to 12 months of transplant.[1,21-23] The incidence of PTLD following SOT ranges from about 1% to 10% depending upon the type of organ transplant.[2,25-28] Small bowel transplant appears to be associated with the highest incidence of PTLD, at about 20%.[2,29] More than 50% of PTLD cases following SOT are diagnosed beyond 12 months from the time of transplant.[26,28,30,31] The incidence of PTLD is generally higher among pediatric patients compared with adults.[2,8,21,29,31] Median survival following a diagnosis of PTLD (after SOT) ranges from

about 10 to 32 months.[8,26,28,32,33] Survival outcomes for PTLD occurring after allogeneic HSCT are poor.[21]

Factors such as EBV and cytomegalovirus (CMV) serology status (of the recipient and the donor), age, type of organ transplant, type of immunosuppressive agents (likely correlated with degree of immunosuppression), and time from transplant, contribute to variations in the risks for developing PTLD.[2,34-37] In patients undergoing allogeneic HSCT, factors associated with increased risks for PTLD included T-cell depletion of the allograft, unrelated or HLA-mismatched grafts, and anti-T-cell therapy (e.g., antithymocyte globulin [ATG] or anti-CD3 monoclonal antibody) for prophylaxis or treatment of graft-versus-host disease (GVHD).[1,20-23] In recipients of SOT, factors associated with increased risks for PTLD included the type of organ transplant (e.g., highest risks in bowel, lung, heart/lung transplants), EBV serology mismatch (i.e., negative recipient/positive donor), CMV serology mismatch (i.e., negative recipient/positive donor), HLA mismatch, and anti-T-cell therapy (e.g., ATG or OKT3) for prevention or treatment of graft rejection.[2,10,31,36-38] Moreover, the use of tacrolimus (compared with cyclosporin) as primary immunosuppressive therapy appeared to increase the risk of PTLD in SOT recipients.[31,38-40] Although CMV disease has also been associated with risks for EBV-positive PTLD, the correlation between CMV infection and development of PTLD is unclear.[37,41,42] In patients with PTLD following SOT, factors such as older age, poor performance status, elevated lactate dehydrogenase (LDH), organ dysfunction, multiple involved lymph nodes, and multi organ involvement were identified as prognostic factors for poorer survival.[7,32,43,44]

The diagnosis and classification of PTLD can be challenging given the nonspecific clinical presentation, and heterogeneity in histopathologic and immunophenotypic presentations. Moreover, subtypes of PTLD

may overlap within the same individual. In the 2008 WHO classification, PTLD are classified into 4 major categories: early lesions, monomorphic PTLD, polymorphic PTLD and classical Hodgkin lymphoma (cHL) type PTLD.[3] Early lesions typically develop within a year of transplantation and are more common in transplant recipients who are EBV naive.[45] Early lesions consist of 2 histological subtypes, plasmacytic hyperplasia and infectious mononucleosis like PTLD.[3] Monomorphic histologies appear to be the most common subtype of PTLD,[28,30,46,47] and resemble one of the B-cell lymphomas (except for indolent lymphomas) or T-cell/NK cell lymphomas seen in immunocompetent individuals. EBV serology status can vary according to lineage; most monomorphic B-cell PTLD are EBV positive whereas most T-cell PTLD are EBV negative.[9,45] Monomorphic B-cell PTLD most commonly resembles diffuse large B cell lymphoma (DLBCL), but some lesions, although less common, can resemble Burkitt lymphoma, plasma cell myeloma or plasmacytoma.[3] Polymorphic PTLD is mostly EBV positive, and can be either polyclonal or monoclonal; this represents the most common type of PTLD among children. cHL-type PTLD is almost always EBV-positive, and is the least common of the PTLD categories.[3]

Diagnosis

Histopathology and adequate immunophenotyping are essential to confirm the diagnosis of PTLD.[3,48,49] Immunophenotyping should include both B-cell and T-cell (as well as NK cell) associated markers. Among B-cell PTLD, expression of BCL6, MUM1 and CD138 can be useful in distinguishing between the histological subtypes of PTLD.[50,51] BCL6 expression was detected in cases of monomorphic PTLD (71% of centroblastic DLBCL), whereas it was consistently absent in polymorphic PTLD. MUM1 was preferentially expressed in 92% of polymorphic PTLD.[50] Overall, BCL6−, MUM1+ and CD138− phenotype is associated most frequently with polymorphic PTLD; BCL6+,

MUM1+/ − and CD138− is mostly associated with monomorphic PTLD.[50,51] The recommended panel for immunohistochemistry (IHC) includes the following markers: CD3, CD5, CD10, BCL6, BCL2, IRF4/MUM1, CD20, CD79a, PAX5, Ki67, and kappa, lambda light chains.. Cell surface markers CD3, CD5, CD7, CD4, CD8, CD19, CD20, CD10, and kappa, lambda are recommended for flow cytometric analysis. Under certain circumstances, the following additional markers may be useful for an IHC panel: CD15, CD30, CD45, CD7, CD4, CD8, ALK, TIA-1, granzyme B, CD57, CD56, and CD138. In addition, the following markers for flow cytometry may also be useful under certain situations: CD138, CD30, CD57, CD56, CD16, CD25, CD52, and cytoplasmic kappa or lambda.

Evaluation of EBV infection status is another essential component of the diagnostic workup. EBV can be detected by either IHC for latent membrane protein 1 (LMP 1) or EBV encoded RNA in situ hybridization (EBER ISH). EBER ISH is more sensitive than immunohistochemistry,[48] and is recommended if EBV-LMP-1 is negative. If immunostaining for EBV-LMP 1 is positive, EBER ISH is not required. Under certain circumstances, EBV evaluation by Southern blot may also be useful.

Immunoglobulin heavy chain (IGH) gene mutations are seen in the majority of B-cell PTLD cases, with the exception of early lesions.[45,51,52] Genetic alterations in MYC, NRAS and TP53 are seen only in monomorphic PTLD.[45,53] BCL6 mutations have been associated with shorter survival and poor response to therapy.[54] In certain situations, molecular genetic analysis to detect IGH rearrangements and BCL6 gene mutations could be useful.

Workup

The initial workup for PTLD should include a physical examination and evaluation of performance status. Laboratory assessments should

include standard blood work including CBC with differential and a metabolic panel (to include albumin, electrolytes, BUN, and creatinine), in addition to measurements of serum LDH levels. Bone marrow evaluations may be useful in selected cases. Prior history of immunosuppressive therapy should also be assessed. CT scans of chest, abdomen and pelvis should be performed. PET CT scan and brain MRI may be useful in selected cases. In addition, MUGA scan/echocardiogram may be useful in cases where treatment with anthracycline or anthracenedione-containing regimens is being considered. Hepatitis B virus (HBV) testing should be performed prior to initiation of treatment with immunotherapy (with or without chemotherapy) given the potential risks for viral reactivation with such regimens. Evaluation of EBV viral load by quantitative PCR can aid in the diagnosis as well as monitoring of treatment responses in patients with PTLD. Plasma or peripheral blood mononuclear cells (PBMC) are useful for measuring EBV viral load, although some studies have shown that viral load in plasma is more sensitive than PBMC in the diagnosis of PTLD.[55-57] EBV serology to assess primary infection versus reactivation may be useful. As previously mentioned, CMV infection has also been associated with an increased risk of PTLD in EBV seronegative patients.[37,41] Thus, PCR for the measurement of EBV and CMV can be useful for selected patients.

Treatment

While guidelines have been published, the optimal treatment for PTLD is not well defined due to the lack of randomized controlled trials and the heterogeneity of the disease.[58] Published reports of treatment for PTLD have included reduction in immunosuppression (RI), use of antiviral agents, single-agent treatment with rituximab, chemotherapy, and/or chemoimmunotherapy regimens; treatment approaches are largely dependent on the PTLD subtype. In general, RI remains the

initial step in the management of nearly all cases of PTLD.[2,44,58,59] In a prospective phase II study that evaluated a sequential approach to therapy (i.e., RI first, then interferon-alfa for less than complete remission (CR), then multiagent chemotherapy if less than CR to interferon) for adults with PTLD following SOT (N=20; n=16 evaluable), RI alone resulted in only one partial remission (PR).[60] The remaining patients experienced either disease progression or graft rejection. One patient achieved a CR with interferon, and among patients eligible for multiagent chemotherapy, 67% achieved a CR. Rituximab was not evaluated as part of this study.[60] The role of antiviral therapy is controversial since the majority of PTLD are associated with latent EBV. Replicating EBV DNA has been reported in about 40% of EBV associated lymphoproliferative disorders in immunocompromised patients.[61,62] Antiviral drugs targeting EBV replication may be beneficial in this subset of patients with early or polymorphic PTLD.[63]

Several phase II studies and retrospective analyses have confirmed the efficacy of rituximab monotherapy in the treatment of patients with B-cell PTLD.[64-70] In a prospective multicenter phase II study in patients with PTLD after SOT (N=46; n=43 evaluable), rituximab induced responses in 44% of patients (CR in 28%) with a 1-year overall survival (OS) rate of 67%.[65] Another prospective multicenter phase II study demonstrated that extended treatment with rituximab (e.g., 2 courses of rituximab) induced a high rate of CR (60.5%; including patients treated with a second course) in patients with PTLD after SOT (N=38) without increasing toxicity.[71] Among the patients who could not achieve a CR with rituximab alone and subsequently received rituximab combined with chemotherapy (R-CHOP or R-EPOCH; n=8), 6 patients achieved a CR (75%). At a median follow up of 27.5 months, the event-free survival and OS rates were 42% and 47%, respectively.[71] In a multicenter retrospective analysis of data from patients with PTLD following SOT

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(N=80), all patients had received initial RI, and 74% were treated with rituximab with or without chemotherapy.[67] The 3-year progression-free survival (PFS) and OS rates for all patients were 57% and 62%, respectively. Inclusion of rituximab as part of initial therapy significantly improved both 3-year PFS (70% vs. 21%) and OS (73% vs. 33%) rates compared with the group who did not receive rituximab.[67]

Anthracycline based chemotherapy with or without rituximab has also been effective in the treatment of patients with PTLD.[43,66,72-75] In a retrospective analysis, CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) induced an overall response rate (ORR) of 65% (CR in 50%) in patients with PTLD after SOT (N=26) who were unresponsive to RI alone.[43] With a median follow up of nearly 9 years, the median OS was 14 months. Treatment-related mortality rate was high, at 31%.[43] Chemotherapy and RT, with or without rituximab has also been reported to induce durable CR with reduced risk of graft impairment when used as first line treatment.[76,77]

As mentioned above, rituximab with or without chemotherapy was shown to improve outcomes in patients with PTLD in a retrospective study.[67] More recently, a prospective multicenter phase II study evaluated the role of sequential chemoimmunotherapy with rituximab (4 weekly doses) followed by CHOP-21 (4 cycles) combined with G-CSF in patients with PTLD who failed initial RI (N=74; n=70 evaluable).[78] The large majority of patients presented with monomorphic histology (primarily DLBCL), and 44% of cases were EBV positive. The ORR with rituximab (n=70) was 60% (CR in 20%), which improved to 90% (CR in 68%) in the patients who received subsequent CHOP chemotherapy following rituximab (n=59). Median response duration has not yet been reached. The median PFS and OS were 4 years and 6.6 years, respectively; the 5-year PFS and OS rates were 50% and 55%, respectively.[78] The most common grade 3 or 4 toxicities included

leukopenia (68%) and infectious events (41%). Treatment-related mortality associated with CHOP was reported in 11% of patients.[78] This trial was amended to introduce a risk-stratified treatment strategy based upon initial response to rituximab, whereby low-risk patients (defined as those achieving CR after initial rituximab) received consolidation with rituximab monotherapy and high-risk patients (defined as non-CR after initial rituximab) received chemoimmunotherapy with R-CHOP-21 (4 cycles) combined with G-CSF.[79] Among the patients enrolled in the risk-stratified protocol (N=91; n=80 evaluable), the ORR was 93% (CR in 78%). The CR rate after initial rituximab alone was 27%. In this low-risk group (who subsequently received rituximab consolidation; n=23), the rate of relapse after a median follow up of more than 3 years was 13%. Among patients with progressive disease after initial rituximab (n=23), sequential therapy with R-CHOP resulted in CR in 65%; this CR rate was higher than that of patients with progressive disease (following initial rituximab) who received sequential CHOP in the original study protocol (CR in 27%).[79] The 3-year OS with the risk-stratified approach was 70%, which compared favorably to the OS rate of 61% (although not statistically different) with the original protocol. This risk-stratified sequential treatment strategy spared the need for chemotherapy in low-risk PTLD patients, while incorporating a more effective chemoimmunotherapy regimen (R-CHOP) in high-risk patients.[79]

Adoptive immunotherapy using autologous or allogeneic EBV specific cytotoxic T lymphocytes (EBV CTLs) has been investigated in several studies.[80-85] In small studies, the use of autologous EBV-CTLs has been shown to prevent the occurrence of PTLD in SOT recipients who were considered at high risk for developing PTLD.[80,85] In patients who underwent allogeneic HSCT, the use of allogeneic EBV-CTLs successfully prevented PTLD in all patients (N=39).[84] In a subsequent study that evaluated the effectiveness of allogeneic EBV-CTLs in a

larger series of patients (including those reported in the earlier Rooney et al, 1998 study) who underwent allogeneic HSCT (N=114), EBV-CTLs prevented PTLD in all patients (n=101) and induced a durable CR in 85% of patients in the subgroup with existing PTLD (n=13).[83] This study also showed that during long-term follow up, functional EBV-CTLs persisted up to 9 years. A prospective multicenter phase II study evaluated allogeneic EBV-CTLs in the treatment of patients with PTLD that failed conventional therapy (N=33).[82] The majority of patients (94%) had received SOT; the remaining patients had undergone allogeneic HSCT. All patients had RI as part of initial therapy for PTLD, and some patients had also received treatment with rituximab, anti-virals, or chemotherapy. The ORR at 6 months was 52% (CR in 42%). The OS rate at 6 months was 79%.[82] Results from this study suggest that immunotherapy with EBV-CTLs may be a promising strategy in patients with PTLD who fail conventional treatments. However, further prospective studies are needed to better define the role of adoptive immunotherapy in the prevention and management of PTLD.

NCCN Recommendations

First-line Treatment and Initial Response

Treatment options for PTLD depend on the histological subtype and should be individualized. RI, if possible, should be a part of the initial treatment approach for all patients with PTLD. It should be noted that response to RI is variable, and patients should be closely monitored during RI. Importantly, RI should be initiated and managed in coordination with the transplant team in order to minimize risks for graft rejection.

For patients with early lesions, first-line management could involve RI alone. For patients who achieve a CR with this approach, re-escalation of immunosuppressive should be individualized, taking into account the extent of initial RI and the nature of the organ allograft; these decisions

should be made in conjunction with the transplant team.[35,60,86] EBV viral load can be monitored by PCR assays. Patients with early lesions who have persistent or progressive disease with RI alone should be managed with second-line therapy options (see section below).

For patients with localized polymorphic PTLD, treatment should include RI, if possible, along with RT with or without rituximab, surgery with or without rituximab, or rituximab alone. For patients with systemic polymorphic PTLD, the NCCN Guidelines panel recommends RI, if possible, along with rituximab alone or rituximab as part of a chemoimmunotherapy regimen (concurrent or sequential combination). In patients with (systemic or localized) polymorphic PTLD who achieve a CR with initial therapy, the patient should either be observed or continue RI (if possible) with or without rituximab maintenance. Patients who have persistent or progressive disease with initial therapy should be managed with second-line treatment options (see section below).

The treatment approach for patients with monomorphic PTLD should be based on the standard treatment regimens used for the unique histology. The treatment options include RI, if possible, and/or rituximab alone or rituximab as part of a chemoimmunotherapy regimen (concurrent or sequential regimen); rituximab alone should only be considered as part of a step-wise approach to treatment in patients who are not highly symptomatic or in those who cannot tolerate chemotherapy due to comorbid conditions. Patients who achieve a CR with initial therapy should undergo surveillance/follow up according to the Guidelines specific for the histology. Patients who have persistent or progressive disease with initial therapy should be managed with second-line treatment options (see section below).

Second line Treatment

Treatment options in the second-line setting are dependent on the response to initial treatment and the histological subtype. For patients with early lesions who have persistent or progressive disease with RI alone, rituximab is recommended as second-line therapy.

For polymorphic PTLD, chemoimmunotherapy or EBV CTL infusion (if EBV positive) are included as options for patients who experience persistent or progressive disease with initial therapy. Participation in a suitable clinical trial, where available, should also be considered in this setting.

For patients with monomorphic PTLD with persistent or progressive disease with initial therapy, second line treatment options are dependent on prior therapy. Rituximab or chemoimmunotherapy regimens are options for patients who received RI alone as initial treatment, whereas patients who received single-agent rituximab as initial therapy should be treated with chemoimmunotherapy. In both situations, other options include participation in a suitable clinical trial, if available, or incorporation of EBV CTL infusion (if EBV positive).

References

1. Curtis RE, Travis LB, Rowlings PA, et al. Risk of lymphoproliferative disorders after bone marrow transplantation: a multi-institutional study. Blood 1999;94:2208-2216. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10498590.

2. Jacobson CA, LaCasce AS. Lymphoma: risk and response after solid organ transplant. Oncology (Williston Park) 2010;24:936-944. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21138175.

3. Swerdlow SH, Webber SA, Chadburn A, Ferry JA. Post-transplant lymphoproliferative disorders. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008.

4. Wagner H-J, Rooney CM, Heslop HE. Diagnosis and treatment of posttransplantation lymphoproliferative disease after hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2002;8:1-8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11846351.

5. Berg LC, Copenhaver CM, Morrison VA, et al. B-cell lymphoproliferative disorders in solid-organ transplant patients: detection of Epstein-Barr virus by in situ hybridization. Hum Pathol 1992;23:159-163. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1310951.

6. Leblond V, Sutton L, Dorent R, et al. Lymphoproliferative disorders after organ transplantation: a report of 24 cases observed in a single center. J Clin Oncol 1995;13:961-968. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7707124.

7. Leblond V, Dhedin N, Mamzer Bruneel MF, et al. Identification of prognostic factors in 61 patients with posttransplantation lymphoproliferative disorders. J Clin Oncol 2001;19:772-778. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11157030.

8. Morrison VA, Dunn DL, Manivel JC, et al. Clinical characteristics of post-transplant lymphoproliferative disorders. Am J Med 1994;97:14-24. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8030652.

9. Herreman A, Dierickx D, Morscio J, et al. Clinicopathological characteristics of posttransplant lymphoproliferative disorders of T-cell origin: single-center series of nine cases and meta-analysis of 147 reported cases. Leuk Lymphoma 2013. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23402267.

10. Knight JS, Tsodikov A, Cibrik DM, et al. Lymphoma after solid organ transplantation: risk, response to therapy, and survival at a transplantation center. J Clin Oncol 2009;27:3354-3362. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19451438.

11. Leblond V, Davi F, Charlotte F, et al. Posttransplant lymphoproliferative disorders not associated with Epstein-Barr virus: a distinct entity? J Clin Oncol 1998;16:2052-2059. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9626203.

12. Nelson BP, Nalesnik MA, Bahler DW, et al. Epstein-Barr virus-negative post-transplant lymphoproliferative disorders: a distinct entity? Am J Surg Pathol 2000;24:375-385. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10716151.

13. Craig FE, Johnson LR, Harvey SA, et al. Gene expression profiling of Epstein-Barr virus-positive and -negative monomorphic B-cell posttransplant lymphoproliferative disorders. Diagn Mol Pathol 2007;16:158-168. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17721324.

14. Morscio J, Dierickx D, Ferreiro JF, et al. Gene Expression Profiling Reveals Clear Differences Between EBV-Positive and EBV-Negative Posttransplant Lymphoproliferative Disorders. Am J Transplant 2013. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23489474.

15. Chadburn A, Suciu-Foca N, Cesarman E, et al. Post-transplantation lymphoproliferative disorders arising in solid organ transplant recipients

are usually of recipient origin. Am J Pathol 1995;147:1862-1870. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7495309.

16. Gulley ML, Swinnen LJ, Plaisance KT, Jr., et al. Tumor origin and CD20 expression in posttransplant lymphoproliferative disorder occurring in solid organ transplant recipients: implications for immune-based therapy. Transplantation 2003;76:959-964. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14508361.

17. Peterson MR, Emery SC, Yung GL, et al. Epstein-Barr virus-associated posttransplantation lymphoproliferative disorder following lung transplantation is more commonly of host origin. Arch Pathol Lab Med 2006;130:176-180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16454557.

18. Petit B, Le Meur Y, Jaccard A, et al. Influence of host-recipient origin on clinical aspects of posttransplantation lymphoproliferative disorders in kidney transplantation. Transplantation 2002;73:265-271. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11821742.

19. Weissmann DJ, Ferry JA, Harris NL, et al. Posttransplantation lymphoproliferative disorders in solid organ recipients are predominantly aggressive tumors of host origin. Am J Clin Pathol 1995;103:748-755. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7785662.

20. Zutter MM, Martin PJ, Sale GE, et al. Epstein-Barr virus lymphoproliferation after bone marrow transplantation. Blood 1988;72:520-529. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2840986.

21. Baker KS, DeFor TE, Burns LJ, et al. New malignancies after blood or marrow stem-cell transplantation in children and adults: incidence and risk factors. J Clin Oncol 2003;21:1352-1358. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12663726.

22. Landgren O, Gilbert ES, Rizzo JD, et al. Risk factors for lymphoproliferative disorders after allogeneic hematopoietic cell transplantation. Blood 2009;113:4992-5001. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19264919.

23. Micallef IN, Chhanabhai M, Gascoyne RD, et al. Lymphoproliferative disorders following allogeneic bone marrow transplantation: the Vancouver experience. Bone Marrow Transplant 1998;22:981-987. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9849695.

24. Omar H, Hagglund H, Gustafsson-Jernberg A, et al. Targeted monitoring of patients at high risk of post-transplant lymphoproliferative disease by quantitative Epstein-Barr virus polymerase chain reaction. Transpl Infect Dis 2009;11:393-399. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19497070.

25. Di Benedetto F, Lauro A, Masetti M, et al. Outcomes after adult isolated small bowel transplantation: experience from a single European centre. Dig Liver Dis 2005;37:240-246. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15788207.

26. Kremer BE, Reshef R, Misleh JG, et al. Post-transplant lymphoproliferative disorder after lung transplantation: a review of 35 cases. J Heart Lung Transplant 2012;31:296-304. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22112992.

27. Taylor AL, Marcus R, Bradley JA. Post-transplant lymphoproliferative disorders (PTLD) after solid organ transplantation. Crit Rev Oncol Hematol 2005;56:155-167. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15979320.

28. Wudhikarn K, Holman CJ, Linan M, et al. Post-transplant lymphoproliferative disorders in lung transplant recipients: 20-yr experience at the University of Minnesota. Clin Transplant 2011;25:705-713. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21077949.

29. Nalesnik M, Jaffe R, Reyes J, et al. Posttransplant lymphoproliferative disorders in small bowel allograft recipients. Transplant Proc 2000;32:1213. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10995914.

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30. Muti G, Cantoni S, Oreste P, et al. Post-transplant lymphoproliferative disorders: improved outcome after clinico-pathologically tailored treatment. Haematologica 2002;87:67-77. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11801467.

31. Opelz G, Dohler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. Am J Transplant 2004;4:222-230. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14974943.

32. Ghobrial IM, Habermann TM, Ristow KM, et al. Prognostic factors in patients with post-transplant lymphoproliferative disorders (PTLD) in the rituximab era. Leuk Lymphoma 2005;46:191-196. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15621801.

33. Oton AB, Wang H, Leleu X, et al. Clinical and pathological prognostic markers for survival in adult patients with post-transplant lymphoproliferative disorders in solid transplant. Leuk Lymphoma 2008;49:1738-1744. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18798108.

34. Post-transplantation lymphoproliferative disorder and OKT3. N Engl J Med 1991;324:1437-1439. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2020303.

35. Swinnen LJ. Transplantation-related lymphoproliferative disorder: a model for human immunodeficiency virus-related lymphomas. Semin Oncol 2000;27:402-408. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10950366.

36. Swinnen LJ, Costanzo-Nordin MR, Fisher SG, et al. Increased incidence of lymphoproliferative disorder after immunosuppression with the monoclonal antibody OKT3 in cardiac-transplant recipients. N Engl J Med 1990;323:1723-1728. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2100991.

37. Walker RC, Marshall WF, Strickler JG, et al. Pretransplantation assessment of the risk of lymphoproliferative disorder. Clin Infect Dis

1995;20:1346-1353. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7620022.

38. Caillard S, Dharnidharka V, Agodoa L, et al. Posttransplant lymphoproliferative disorders after renal transplantation in the United States in era of modern immunosuppression. Transplantation 2005;80:1233-1243. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16314791.

39. Cao S, Cox KL, Berquist W, et al. Long-term outcomes in pediatric liver recipients: comparison between cyclosporin A and tacrolimus. Pediatr Transplant 1999;3:22-26. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10359027.

40. Younes BS, McDiarmid SV, Martin MG, et al. The effect of immunosuppression on posttransplant lymphoproliferative disease in pediatric liver transplant patients. Transplantation 2000;70:94-99. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10919581.

41. Manez R, Breinig MC, Linden P, et al. Posttransplant lymphoproliferative disease in primary Epstein-Barr virus infection after liver transplantation: the role of cytomegalovirus disease. J Infect Dis 1997;176:1462-1467. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9395355.

42. Stevens SJ, Verschuuren EA, Pronk I, et al. Frequent monitoring of Epstein-Barr virus DNA load in unfractionated whole blood is essential for early detection of posttransplant lymphoproliferative disease in high-risk patients. Blood 2001;97:1165-1171. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11222357.

43. Choquet S, Trappe R, Leblond V, et al. CHOP-21 for the treatment of post-transplant lymphoproliferative disorders (PTLD) following solid organ transplantation. Haematologica 2007;92:273-274. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17296588.

44. Tsai DE, Hardy CL, Tomaszewski JE, et al. Reduction in immunosuppression as initial therapy for posttransplant

lymphoproliferative disorder: analysis of prognostic variables and long-term follow-up of 42 adult patients. Transplantation 2001;71:1076-1088. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11374406.

45. Tsao L, Hsi ED. The clinicopathologic spectrum of posttransplantation lymphoproliferative disorders. Arch Pathol Lab Med 2007;131:1209-1218. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17683183.

46. Dierickx D, Tousseyn T, Sagaert X, et al. Single-center analysis of biopsy-confirmed posttransplant lymphoproliferative disorder: incidence, clinicopathological characteristics and prognostic factors. Leuk Lymphoma 2013. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23442063.

47. Majhail NS. Secondary cancers following allogeneic haematopoietic cell transplantation in adults. Br J Haematol 2011;154:301-310. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21615719.

48. Harris NL, Ferry JA, Swerdlow SH. Posttransplant lymphoproliferative disorders: summary of Society for Hematopathology Workshop. Semin Diagn Pathol 1997;14:8-14. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9044505.

49. Parker A, Bowles K, Bradley JA, et al. Diagnosis of post-transplant lymphoproliferative disorder in solid organ transplant recipients - BCSH and BTS Guidelines. Br J Haematol 2010;149:675-692. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20408847.

50. Capello D, Cerri M, Muti G, et al. Molecular histogenesis of posttransplantation lymphoproliferative disorders. Blood 2003;102:3775-3785. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12907442.

51. Capello D, Rossi D, Gaidano G. Post-transplant lymphoproliferative disorders: molecular basis of disease histogenesis and pathogenesis. Hematol Oncol 2005;23:61-67. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16216037.

52. Capello D, Cerri M, Muti G, et al. Analysis of immunoglobulin heavy and light chain variable genes in post-transplant lymphoproliferative disorders. Hematol Oncol 2006;24:212-219. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16897790.

53. Knowles DM, Cesarman E, Chadburn A, et al. Correlative morphologic and molecular genetic analysis demonstrates three distinct categories of posttransplantation lymphoproliferative disorders. Blood 1995;85:552-565. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7812011.

54. Cesarman E, Chadburn A, Liu YF, et al. BCL-6 gene mutations in posttransplantation lymphoproliferative disorders predict response to therapy and clinical outcome. Blood 1998;92:2294-2302. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9746767.

55. Ryan JL, Fan H, Swinnen LJ, et al. Epstein-Barr Virus (EBV) DNA in plasma is not encapsidated in patients with EBV-related malignancies. Diagn Mol Pathol 2004;13:61-68. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15167006.

56. Wagner HJ, Wessel M, Jabs W, et al. Patients at risk for development of posttransplant lymphoproliferative disorder: plasma versus peripheral blood mononuclear cells as material for quantification of Epstein-Barr viral load by using real-time quantitative polymerase chain reaction. Transplantation 2001;72:1012-1019. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11579293.

57. Tsai DE, Douglas L, Andreadis C, et al. EBV PCR in the diagnosis and monitoring of posttransplant lymphoproliferative disorder: results of a two-arm prospective trial. Am J Transplant 2008;8:1016-1024. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18312608.

58. Parker A, Bowles K, Bradley JA, et al. Management of post-transplant lymphoproliferative disorder in adult solid organ transplant recipients - BCSH and BTS Guidelines. Br J Haematol 2010;149:693-705. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20408848.

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59. Reshef R, Vardhanabhuti S, Luskin MR, et al. Reduction of immunosuppression as initial therapy for posttransplantation lymphoproliferative disorder. Am J Transplant 2011;11:336-347. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21219573.

60. Swinnen LJ, LeBlanc M, Grogan TM, et al. Prospective study of sequential reduction in immunosuppression, interferon alpha-2B, and chemotherapy for posttransplantation lymphoproliferative disorder. Transplantation 2008;86:215-222. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18645482.

61. Fan H, Kim SC, Chima CO, et al. Epstein-Barr viral load as a marker of lymphoma in AIDS patients. J Med Virol 2005;75:59-69. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15543571.

62. Katz BZ, Raab-Traub N, Miller G. Latent and replicating forms of Epstein-Barr virus DNA in lymphomas and lymphoproliferative diseases. J Infect Dis 1989;160:589-598. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2551973.

63. Hanto DW, Frizzera G, Gajl-Peczalska KJ, et al. Epstein-Barr virus-induced B-cell lymphoma after renal transplantation: acyclovir therapy and transition from polyclonal to monoclonal B-cell proliferation. N Engl J Med 1982;306:913-918. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6278307.

64. Blaes AH, Peterson BA, Bartlett N, et al. Rituximab therapy is effective for posttransplant lymphoproliferative disorders after solid organ transplantation: results of a phase II trial. Cancer 2005;104:1661-1667. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16149091.

65. Choquet S, Leblond V, Herbrecht R, et al. Efficacy and safety of rituximab in B-cell post-transplantation lymphoproliferative disorders: results of a prospective multicenter phase 2 study. Blood 2006;107:3053-3057. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16254143.

66. Elstrom RL, Andreadis C, Aqui NA, et al. Treatment of PTLD with rituximab or chemotherapy. Am J Transplant 2006;6:569-576. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16468968.

67. Evens AM, David KA, Helenowski I, et al. Multicenter analysis of 80 solid organ transplantation recipients with post-transplantation lymphoproliferative disease: outcomes and prognostic factors in the modern era. J Clin Oncol 2010;28:1038-1046. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20085936.

68. Jain AB, Marcos A, Pokharna R, et al. Rituximab (chimeric anti-CD20 antibody) for posttransplant lymphoproliferative disorder after solid organ transplantation in adults: long-term experience from a single center. Transplantation 2005;80:1692-1698. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16378063.

69. Milpied N, Vasseur B, Parquet N, et al. Humanized anti-CD20 monoclonal antibody (Rituximab) in post transplant B-lymphoproliferative disorder: a retrospective analysis on 32 patients. Ann Oncol 2000;11 Suppl 1:113-116. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10707791.

70. Oertel SHK, Verschuuren E, Reinke P, et al. Effect of anti-CD 20 antibody rituximab in patients with post-transplant lymphoproliferative disorder (PTLD). Am J Transplant 2005;5:2901-2906. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16303003.

71. Gonzalez-Barca E, Domingo-Domenech E, Capote FJ, et al. Prospective phase II trial of extended treatment with rituximab in patients with B-cell post-transplant lymphoproliferative disease. Haematologica 2007;92:1489-1494. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18024397.

72. Buadi FK, Heyman MR, Gocke CD, et al. Treatment and outcomes of post-transplant lymphoproliferative disease: a single institution study. Am J Hematol 2007;82:208-214. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17022049.

73. Buell JF, Gross TG, Hanaway MJ, et al. Chemotherapy for posttransplant lymphoproliferative disorder: the Israel Penn International Transplant Tumor Registry experience. Transplant Proc 2005;37:956-957. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15848588.

74. Fohrer C, Caillard S, Koumarianou A, et al. Long-term survival in post-transplant lymphoproliferative disorders with a dose-adjusted ACVBP regimen. Br J Haematol 2006;134:602-612. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16889621.

75. Orjuela M, Gross TG, Cheung Y-K, et al. A pilot study of chemoimmunotherapy (cyclophosphamide, prednisone, and rituximab) in patients with post-transplant lymphoproliferative disorder following solid organ transplantation. Clin Cancer Res 2003;9:52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14506193.

76. Taylor AL, Bowles KM, Callaghan CJ, et al. Anthracycline-based chemotherapy as first-line treatment in adults with malignant posttransplant lymphoproliferative disorder after solid organ transplantation. Transplantation 2006;82:375-381. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16906036.

77. Trappe R, Hinrichs C, Appel U, et al. Treatment of PTLD with rituximab and CHOP reduces the risk of renal graft impairment after reduction of immunosuppression. Am J Transplant 2009;9:2331-2337. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19663889.

78. Trappe R, Oertel S, Leblond V, et al. Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicentre phase 2 PTLD-1 trial. Lancet Oncol 2012;13:196-206. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22173060.

79. Trappe RU, Dierickx D, Reinke P, et al. Interim analysis of the largest prospective trial to date in adult CD20-positive post-transplant lymphoproliferative disorder (PTLD): Introducing risk-stratified sequential treatment (RSST) [abstract]. J Clin Oncol 2012;30:Abstract 8030. Available at: http://meeting.ascopubs.org/cgi/content/abstract/30/15_suppl/8030.

80. Comoli P, Labirio M, Basso S, et al. Infusion of autologous Epstein-Barr virus (EBV)-specific cytotoxic T cells for prevention of EBV-related lymphoproliferative disorder in solid organ transplant recipients with evidence of active virus replication. Blood 2002;99:2592-2598. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11895798.

81. Haque T, Wilkie GM, Taylor C, et al. Treatment of Epstein-Barr-virus-positive post-transplantation lymphoproliferative disease with partly HLA-matched allogeneic cytotoxic T cells. Lancet 2002;360:436-442. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12241714.

82. Haque T, Wilkie GM, Jones MM, et al. Allogeneic cytotoxic T-cell therapy for EBV-positive posttransplantation lymphoproliferative disease: results of a phase 2 multicenter clinical trial. Blood 2007;110:1123-1131. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17468341.

83. Heslop HE, Slobod KS, Pule MA, et al. Long-term outcome of EBV-specific T-cell infusions to prevent or treat EBV-related lymphoproliferative disease in transplant recipients. Blood 2010;115:925-935. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19880495.

84. Rooney CM, Smith CA, Ng CY, et al. Infusion of cytotoxic T cells for the prevention and treatment of Epstein-Barr virus-induced lymphoma in allogeneic transplant recipients. Blood 1998;92:1549-1555. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9716582.

85. Savoldo B, Goss JA, Hammer MM, et al. Treatment of solid organ transplant recipients with autologous Epstein Barr virus-specific cytotoxic T lymphocytes (CTLs). Blood 2006;108:2942-2949. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16835376.

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86. Swinnen LJ. Diagnosis and treatment of transplant-related lymphoma. Ann Oncol 2000;11 Suppl 1:45-48. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10707778.

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