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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Non-Hodgkin's Lymphomas

Version 1.2011

NCCN.org

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Clinical Trials: The 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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Updated to the 1.2011 version of the Non-Hodgkin's Lymphoma guidelines from the 1.2010 version include:

New Guidelines

NKTL-1
- Extranodal NK/T-cell Lymphoma, nasal type is a new guideline.

PTLD-1
- Post-transplant lymphoproliferative disorders is a new guideline.

Principles of Radiation Therapy
- Principles of radiation therapy is new to the guidelines and links to this page were added throughout the guidelines.

Global change
- Clinical follow-up was modified as "Clinical follow-up every 3-6 mo *for 5 y then yearly* or as clinically indicated" throughout the guidelines.
- Workup sections, "MUGA scan/echocardiogram" was modified by adding "if anthracycline or anthracenediones-based regimen is indicated" which was previously in a footnote.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
- A new algorithm for CLL with deletion of 11q on CSLL-6 and the corresponding suggested regimens on CSLL-D 3 of 5 were added.

CSLL-1
- Diagnosis, the section title "informative for prognostic determination" was modified as "informative for prognostic *and/or therapy* determination".

CSLL-2
- Workup, Hepatitis B testing bullet was modified as "if *CD20 monoclonal antibody* contemplated."
- Workup, "PET scan is generally not useful in CLL but can assist in directing nodal biopsy if Richter's transformation is suspected" was added.

CSLL-3
- Evaluate for indications for treatment, "Progressive" was added to bulky disease.
- Footnote 'j' was modified by adding "... unless above 200- 300 x 10^9/L or symptoms related to leukostatsis." Also for CSLL-5.
- Footnote 'm' was modified by adding, "... FISH *[t(11;14); t(11q;v); +12; del(11q); del(13q); del(17p)*] is *necessary* to direct treatment."
- Footnote n, "In addition to the regimens listed in BCEL-C, R-HyperCVAD has also been used in this setting" is new to the page.

CSLL-4
- CLL without a deletion 11 q was added to the page.
- Age ≥ 70 y, "or younger patients with co-morbidities" was added as a qualifier.
- Footnotes 'o' and 'p' are new to the page.

CSLL-5
- Moved statement from footnote to a subbullet of clinical trial, "17p deletion is associated with low response rates with all treatments and there is no standard treatment, clinical trial is recommended".
- Footnote r, "Patients with low positivity should be retested due to chance of false positive results" is new to the page.

CSLL-A
- Footnote b, "IGHV rearrangements involving VH3-21 carry a poor prognosis even if mutated" is new to the page.
- Percentages were added to outcome association for flow cytometry.

CSLL-C
- Sinopulmonary was added to recurrent infections.
- Recurrent sinopulmonary infections, 2nd subbullet was modified to "...nadir level *of approximately 500 mg/dl*".
- Antiinfective prophylaxis, alemtuzumab subbullet was modified by adding, "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 present, others 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."
- Autoimmune cytopenia, PRCA, "and bone marrow evaluation" was added.
- Vaccination, pneumococcal vaccine was modified by adding "Prevnar preferred"
- Blood product support, "irradiate all blood products" was modified by adding "to avoid transfusion associated GVHD".

CSLL-D 1 of 5
- CLL without del (11q) or del (17p)
  - First-line therapy, age ≥ 70 y or younger patients with co-morbidities
    - Vincristine was removed from combination with CP ± rituximab.
    - "+ rituximab" was added to bendamustine.
    - Cladrabine was added.
  - First-line therapy, age < 70 y or older patients without significant co-morbidities
    - Bendamustine + rituximab was added.
    - "Alemtuzumab, chlorambucil, bendamustine, fludarabine" as monotherapies were removed.
  - Relapsed/refractory therapy, short response < 2 y for age ≥ 70 y:
    - Chlorambucil ± prednisone, "if used first-line" was added as a qualifier.
    - Alemtuzumab ± rituximab was added.

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Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (cont)

CSLL-D 2 of 5

- CLL with del (17p)
  - First-line therapy
    - "± rituximab" was added to alemtuzumab and 'rituximab" was added to bendamustine.
  - Relapsed/refractory therapy
    - "± rituximab" was added to bendamustine and high-dose dexamethasone and corresponding footnote g, "Rituximab should be added unless patient is known to be refractory to rituximab" was added.
    - Footnote f, "This is not effective in patients with lymph nodes > 5 cm" was added to ofatumumab.

Follicular Lymphoma

FOLL-1

- Diagnosis, useful under certain circumstances, "Paraffin section immunohistochemistry: Ki67" and corresponding footnote f, "There are reports showing Ki67 proliferation fraction of > 30 % may be associated with a more aggressive clinical behavior but no evidence this should guide treatment decisions" were added.

FOLL-2

- Stage I, II locoregional RT (preferred) was modified as "IFRT (preferred for clinical stage I or contiguous stage II)".
- Bulky Stage II or abdominal disease was modified as "Stage IIX".
- Footnote q, "Consider clinical trials appropriate for patients on observation" is new to the page.

FOLL-B 1 of 3

- First-line therapy, "bendamustine + rituximab" the category was changed from a category 2A to a category 1 designation.
- First-line therapy for elderly or infirm, "± rituximab" was added to single agent alkylators.
- First-line consolidation or extended dosing, "rituximab maintenance" the category designation was changed from category 2B to a category 1 and "up to 2 y" was added as a qualifier.
- "High dose therapy with autologous stem cell rescue" and "allogeneic stem cell transplant for highly selected patients"and "rituximab maintenance" were added to a new section titled "Second-line Consolidation or Extended Dosing".

Gastric MALT Lymphoma

MALT-1

- Workup
  - "Endoscopic ultrasound (if available)" was moved to essential with endoscopy.
  - "SPEP" was added to useful under certain circumstances. (Also for NGMLT-1)

MALT-2

- For Stage I_{E2} or Stage II_E, initial therapy of currently accepted antibiotic therapy for H. pylori followed by evaluation for H. pylori eradication with endoscopy was added.
- Footnote h, "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" is new to the page.

MALT-3

- Footnote q, "If patient originally had clinical Stage I_{E2} or Stage II_E early RT should be considered if there is no response to antibiotics" is new to the page.

MALT-4

- Restage after RT was changed from 3 mo to 3-6 mo.
- For lymphoma positive and H. Pylori negative or positive, "locoregional RT, if not previously treated" was removed and directed to follicular lymphoma.

Nongastric MALT lymphoma

NGMLT-1

- Workup, useful in selected cases, "SPEP" was added. Also for NODE-1.

Nodal Marginal Zone Lymphoma

NODE-1

- Diagnosis, the section title "useful under certain circumstances" was modified by adding "for clarification of diagnosis".

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Splenic Marginal Zone Lymphoma

SPLN-1

- Diagnosis, essential, "peripheral blood, bone marrow, or tissue" was added to "cell surface marker analysis by flow cytometry".
- Footnote 'a' is new to the page.
- Workup, useful in selected cases, "direct Coombs test" was added.

SPLN-2

- Hepatitis C, "assess" was added as a first decision in management and if no symptoms, then "observe" was added.
- Footnote, "Splenectomy is preferred in patients who are able to tolerate it" was removed and footnote e, "Vaccination should be performed at least 2 weeks before splenectomy" was added to the page.

Mantle Cell Lymphoma

MANT-1

- Footnote c, "Ki67 proliferation fraction of < 30% is associated with a more favorable prognosis. However, it is not used to guide treatment" is new to the page.
- Footnote 'e' was modified by adding, "essential for confirmation of stage I- II diseaese".

MANT-2

- Bulky Stage II or abdominal disease was modified as "Stage IIX".
- Stage IIX, III, IV, for induction therapy with suggested treatment regimens, "± RT" was removed.
- Footnote 'i' is a new reference.

MANT-A 1 of 3

- Induction therapy,
  - Aggressive therapy, "CALGB regimen (rituximab + methotrexate with augmented CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone])" and "Sequential RCHOP/RICE (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (rituximab,ifosfamide, carboplatin, etoposide)" were added as treatment options.
  - Less aggressive therapy,
    - "CVP ± rituximab" was added as an option.
    - Cladribine was changed from "± rituximab" to "+ rituximab".
- Second-line therapy
  - "± rituximab" was added to lenalidomide.
  - Cladribine was changed from "± rituximab" to "+ rituximab".
  - "Temsirolimus" and "thalidomide + rituximab" were removed.

Diffuse Large B-Cell Lymphoma

BCEL-1

- Subtypes included with DLBCL were added:
  - 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
- Subtypes not included with DLBCL were added:
  - Primary DLBCL of the CNS

BCEL-3

- Stage I - IV, "RCHOP 6 or 8 cycles" was revised to "RCHOP 6 cycles". Also for follow-up on BCEL-5.
- Stage I, II, "locoregional RT" was changed to "RT".
- Stage II, IV, "preferred" was removed from "clinical trial".
- Footnote 'k' was modified by adding, "See AIDS-2 for HIV-positive DLBCL."

BCEL-4

- Partial response, "± RT pre- or post-transplant" was added to "High dose therapy with autologous stem cell rescue" and "Clinical trial (may include allogeneic stem cell transplant."
- For completion of planned course of treatment after a complete response, the algorithm has been directed to "clinical followup every 3-6 mo..." rather than "end of treatment restaging."

BCEL-5

- For stage III, IV, interim restaging was changed from "after 3-4 cycles" to "after 2-4 cycles".
- After completion of treatment with a complete response, "Observation (preferred)" and "For high risk patients, high dose therapy can be considered (category 2B)" were added as further options.

BCEL-C 1 of 3

- First-line therapy for patients with poor left ventricular function, "RCEOP " was added as a treatment option.
- Second-line therapy "for candidates for high dose therapy with autologous stem cell rescue" was clarified as "*For patients with intention to proceed to* high dose autologous stem cell rescue."
- Second-line therapy for patients who are non-candidates for high dose therapy,
  - "CEOP ± rituximab" and "GDP ± rituximab" and "GemOx ± rituximab" were added.
  - "± rituximab" was added to lenalidomide.
- Footnote 'e' is new to the page.

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Burkitt Lymphoma

BURK-1

- Diagnosis, useful under certain circumstances, for additional immunohistochemical studies to establish lymphoma subtype, "Frozen: kappa/lambda" and "Paraffin panel: TdT; kappa/lambda" were removed.
- Workup, "flow cytometry of cerebrospinal fluid" was moved from useful under certain circumstances to essential. (Also for BLAST-1)

BURK-2

- "Second line chemotherapy followed by high dose chemotherapy with HSCT in selected patients" was added as a treatment option for relapse after a complete response in the low risk category and after consolidation in a clinical trial for the high risk category.

BURK-A 1 of 2

- For "dose-adjusted EPOCH" in both low and high risk combination regimens, a statement, "data is for patients without CNS disease" was added.
- "Second line therapy options for relapse for select patients with reasonable remission" was added with the following regimens:
  - Dose-adjusted EPOCH
  - R-IVAC if have not received previously
  - RGDP
  - HDAC

AIDS-Related B-cell lymphoma

AIDS-1

- Workup, "stool guaiac, if anemic" was removed.

AIDS-2

- Statement regarding antiretrovirals was added, "Antiretrovirals can be administered safely with chemotherapy, however some regimens have recommended discontinuation. Any change in antiviral therapy should be done in consultation with infectious disease specialist." (Also for AIDS-3)
- For lymphoma-associated with Castleman's disease, DLBCL, and Primary effusion lymphoma, "For DLBCL relapse, see BCEL-6" was added.

AIDS-3

- For primary CNS lymphoma, "For select patients with good performance status and on HAART, see NCCN CNS Guidelines- Primary CNS Lymphoma" was added.
- Footnote g, "Management can also apply to HIV negative plasmablastic lymphoma" was added to the page.

Primary Cutaneous B-Cell Lymphoma

- "Locoregional RT" was clarified as "local RT" in the primary cutaneous B-cell lymphoma guidelines.

CUTB-1

- Diagnosis, useful under certain circumstances, "Assessment of surface IgM and IgD expression (to further help in distinguishing DLBCL, leg type from FCL)" was added.
- Statement was added, "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."
- Workup, peripheral blood flow cytometry, "if CBC demonstrates lymphocytosis" was added.
- Footnote 'c' with the typical immunophenotype was added.
- Footnote 'd' was modified, "Rule out drug-induced *cutaneous lymphoid hyperplasia".*

CUTB-2

- Solitary/regional, initial therapy, "preferred" was added to local RT.
- Generalized disease, initial therapy:
  - "intralesional steroids" was added. Also for CUTB-3.
  - palliative chemotherapy, '± rituximab" was added to "chlorambucil". Also for CUTB-3.
- Footnote j, was modified by adding "*There are case reports showing efficacy of* topicals which include...". Also for CUTB-4.

CUTB-4

- For solitary/regional and generalized disease with a complete response after initial therapy, "observe" was added until relapse.
- Solitary/regional, secondary therapy, "local RT" was modified by adding "to previously unirradiated tumor".

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Peripheral T-Cell Lymphomas

TCEL-1
- Diagnosis, useful under certain circumstances: "PD1" and "βF1 and CD279" were added.

TCEL-3
- Induction therapy for "ALCL, ALK positive" subtype was added.

TCEL-4
- Partial response, follow-up therapy, "± RT" was added to "high dose therapy with stem cell transplant" and "clinical trial (may include allogeneic stem cell transplant".

TCEL-B 1 of 2
- First-line therapy, the following list of "Other regimens that can be used" were added:
  - CHOEP
  - CHOP every 2 or 3 wks
  - CHOP followed by ICE
  - CHOP followed by IVE
  - HyperCVAD alternating with high-dose methotrexate and cytarabine
- Footnote b, "Standard induction for PTCL remains undefined with the exception of ALCL, ALK + for which CHOP remains the standard. Clinical trial is preferred for all other subtypes" is new to the page.
- Footnote c, "In AITL, pralatrexate has limited activity" is new to the page.
- Footnote e, "With close follow-up of renal function" is new to the page.

Mycosis Fungoides/Sezary Syndrome

MFSS-1
- Workup, useful in selected cases: "Rebiopsy if suspicious of large cell transformation" was added.
- Workup, essential, "chest x-ray" was removed from imaging studies.
- Footnote 'a' was modified by adding "clinically or histologically non-daignostic cases".
- Footnote 'c' was modified by adding "demonstration of identical clones in skin, blood and/or lymph node may be helpful in selected cases".

MFSS-2
- Footnote 'g' was modified as "...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 more or increase in CD4 cells with an abnormal phenotype (40% CD4/CD7 or 30% CD4/CD26)."

MFSS-4
- Stage IA, for primary treatment, "If B1 blood involvement, consider primary treatment for Stage IIIB B1 (category 2B)" was added. Also for IB-IIA on MFSS-5.

MFSS-6
- "and/or histologic evidence of folliculotropic or large cell transformation (LCT)" was added with "stage IIB."
- Limited extent tumor, primary treatment with local RT for limited extent tumor, transformed, and/or folliculotrophic disease, "+ skin-directed therapies" was removed and "± skin-directed therapies" was added to "systemic therapies ± RT".
- Footnotes s, "Rebiopsy if suspect large cell transformation" is new to the page.
- Footnote t, "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 category A or B are appropriate. If aggressive growth is seen, then agents listed in category C (SYST-CAT C) are preferred" is new to the page.
- Footnote 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" is new to the page.
- Footnote y, "The role of allogeneic HSCT is controversial. See discussion for further details" is new to the page. Also for MFSS-7 and MFSS-8.

MFSS-7
- Footnote cc, "Alemtuzumab can be administered by IV or subcutaneously. Lower doses administered subcutaneously have shown lower incidence of infectious complications" is new to the page. Also for MFSS-8.

MFSS-8
- For primary treatment of non sezary or visceral disease, a link to the new category C treatment options for systemic therapies was added.

MFSS-A 1 of 3
- Systemic therapies, a new group titled "Category C" was added with corresponding footnote g, "Combination regimens are generally reserved for patients with relapsed/refratory or extracutaneous disease."

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Adult T-cell Leukemia/Lymphoma

ATLL-1

- **Diagnosis, useful under certain circumstances, "Molecular analysis HTLV-1 clonal integration is encouraged in all cases of mature T-cell lymphoma/leukemia in HTLV-1 seropositive individuals: Southern blot or inverse PCR" was removed.**

ATLL-2

- **Chronic/smoldering subtype, after persistent or progressive disease "discontinue treatment" was removed and "clinical trial or best supportive care" were added as additional treatment options.**

ATLL-3

- **Acute subtype, after complete response "consider allogeneic stem cell transplant" was added as an additional treatment option.**
- **Both acute and lymphoma subtypes, after persistent or progressive disease "best supportive care" was added as an additional treatment option.**

Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms

NHODG-A

- **Footnote c, "Rare cases of both cyclin D1 and t(11;14) negative MCL have been reported. This diagnosis should be made with extreme caution and with expert consultation" was added.**

Tumor Lysis Syndrome

NHODG-B

- **High risk features for tumor lysis syndrome were added.**
- **Indications for rasburicase use were added.**

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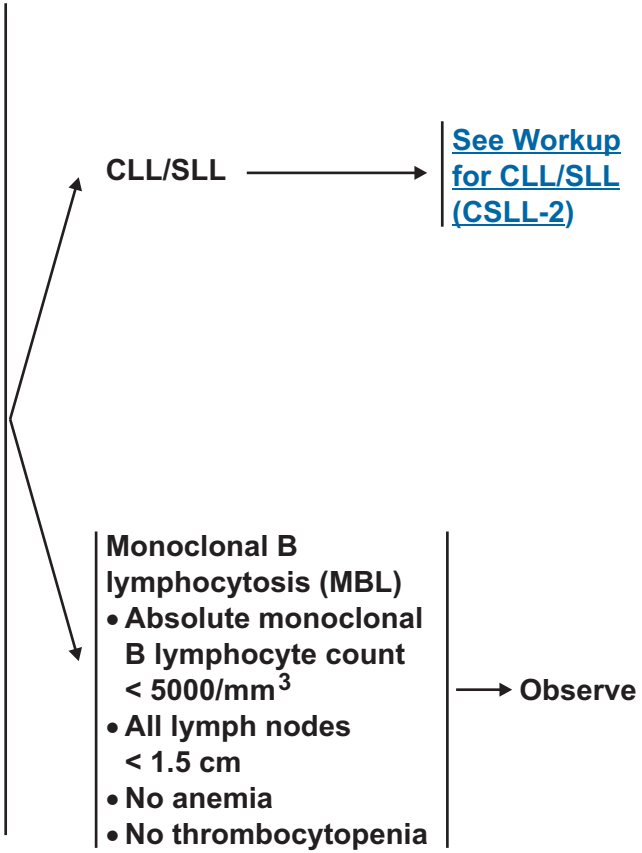
DIAGNOSIS

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.**
- **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. This is particularly true for the diagnosis of CLL/SLL.**
- **Flow cytometry of blood adequate for diagnosis of CLL/SLL (biopsy not required).**
- **Adequate immunophenotyping to establish diagnosis[b,c]**
  - **Recommended panel for paraffin section immunohistochemistry: CD3, CD5, CD10, CD20, CD23, cyclin D1**
    or
  - **Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10**
- **Absolute monoclonal B lymphocyte count[d]**

INFORMATIVE FOR PROGNOSTIC AND/OR THERAPY DETERMINATION:[e]

- **Cytogenetics and/or FISH to detect: t(11;14); t(11q;v); +12; del(11q); del(13q); del(17p)**
- **Molecular genetic analysis to detect: immunoglobulin heavy chain variable gene (IGHV) mutation status**
- **Determination of CD38 and Zap 70 expression by flow cytometry or immunohistochemistry[f]**



[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 and Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-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 monoclonal B lymphocytosis (MBL).

[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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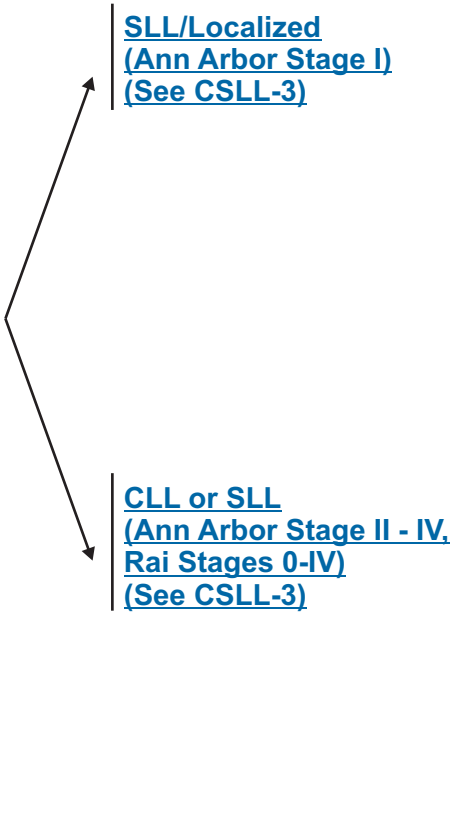
WORKUP

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
- LDH
- Comprehensive metabolic panel
- Hepatitis B testing[g] if CD20 monoclonal antibody contemplated
- MUGA scan/echocardiogram if anthracycline or anthracenediones-based regimen is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Quantitative immunoglobulins
- Reticulocyte count, hepatoglobin, 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
- 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



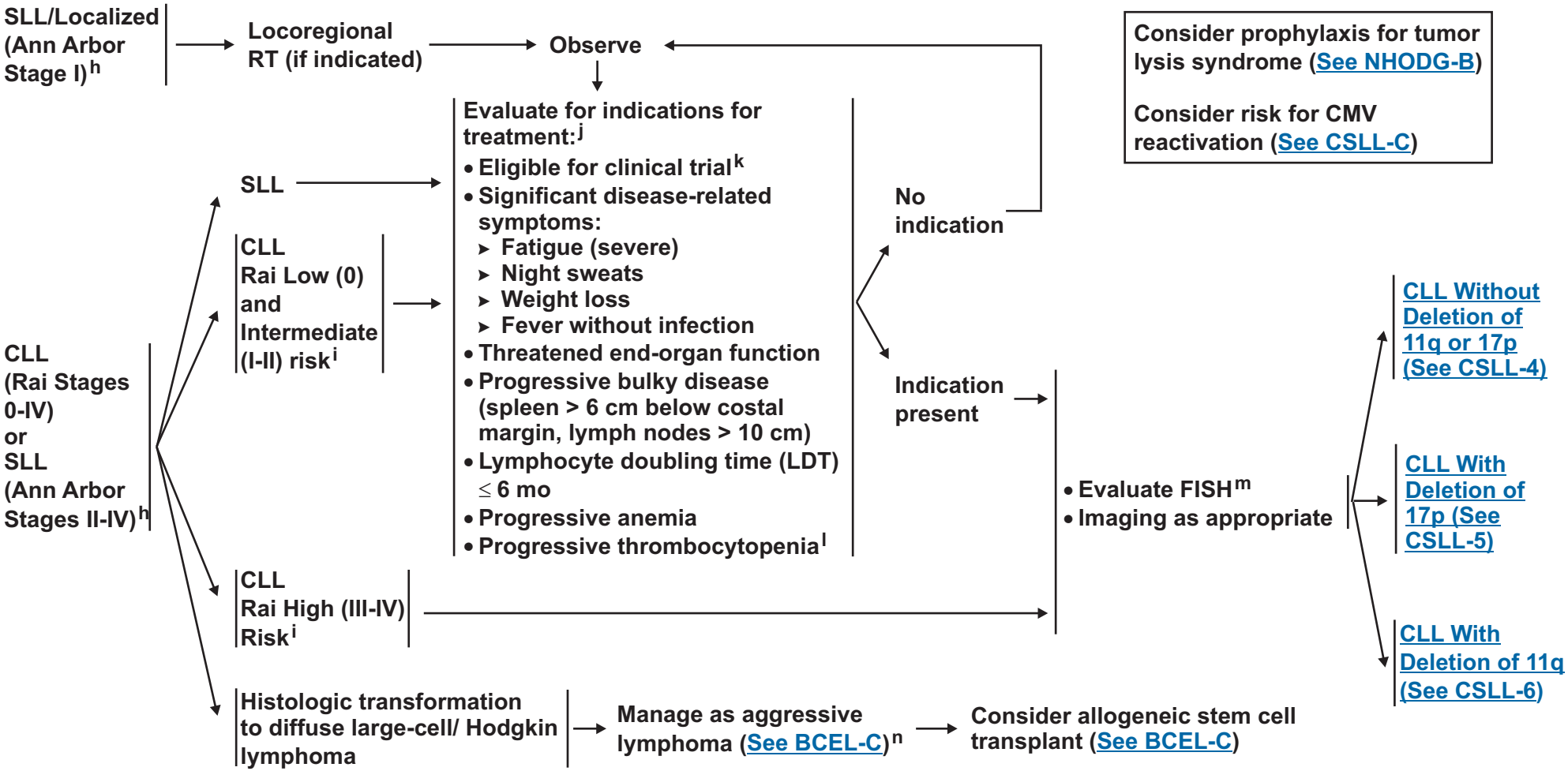
[g] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check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

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PRESENTATION



[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 leukostatsis.

[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] Re-evaluation of FISH [t(11;14); t(11q;v); +12; del(11q); del(13q); del(17p)] is necessary to direct treatment.

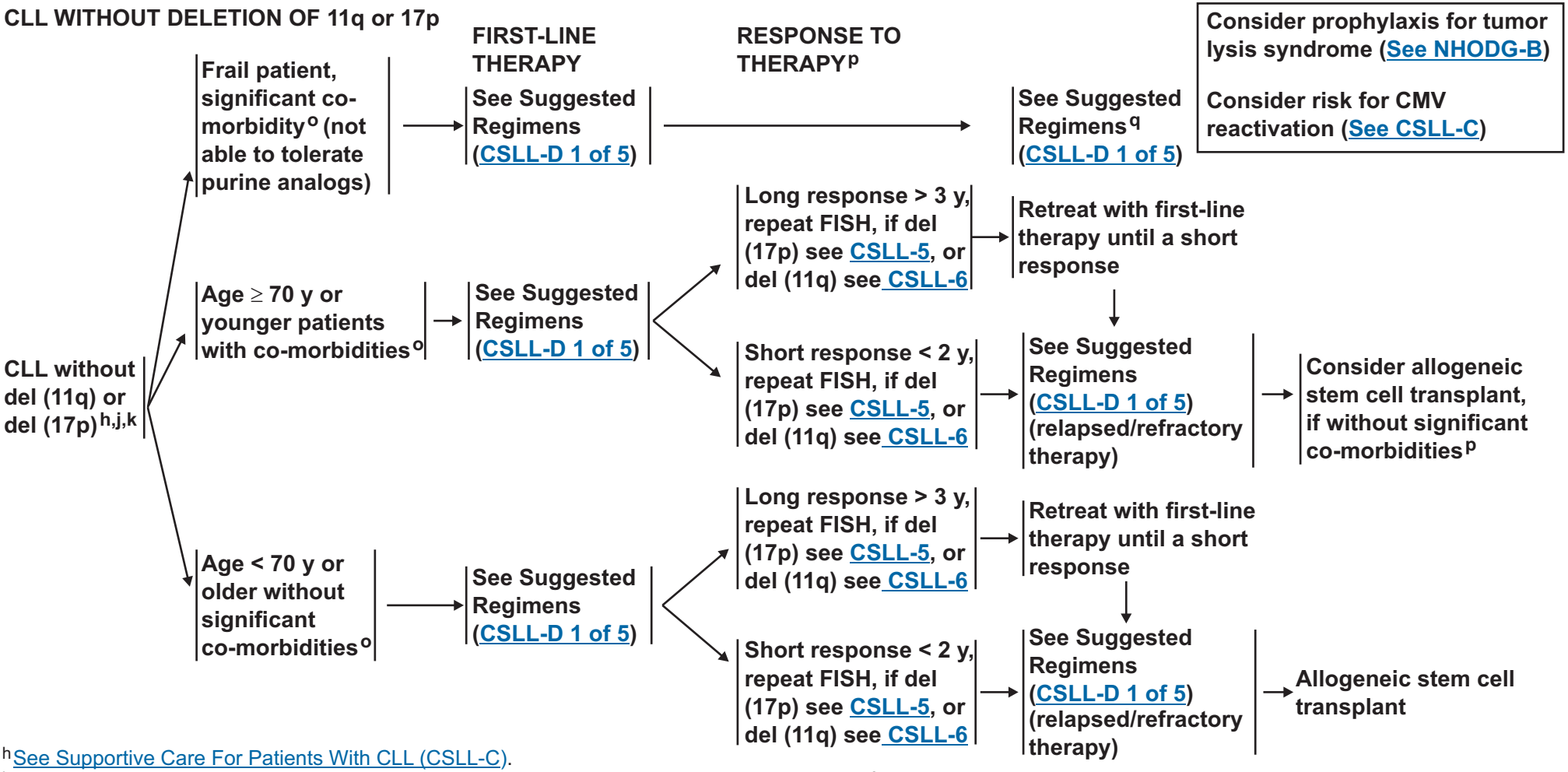
[n] In addition to the regimens listed in BCEL-C, R-HyperCVAD has also been used in this setting.

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CLL WITHOUT DELETION OF 11q or 17p



[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 leukostatsis.

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

[o] 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.

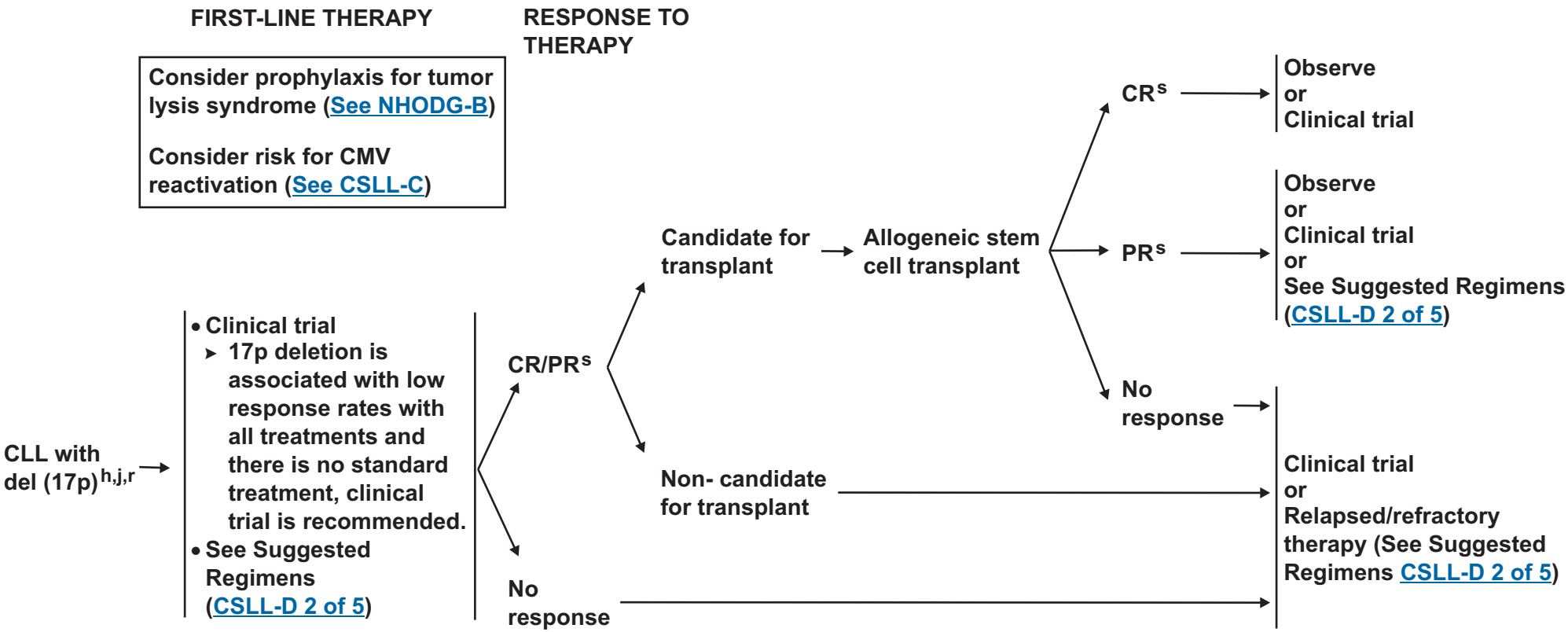
[p] Keating M, Wierda W, Tam C, et al. Long term outcome following treatment failure of FCR chemoimmunotherapy as initial therapy for chronic lymphocytic leukemia. Blood (ASH Annual Meeting Abstracts) 2009;114:Abstract 2381.

[q] 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 WITH DELETION OF 17p

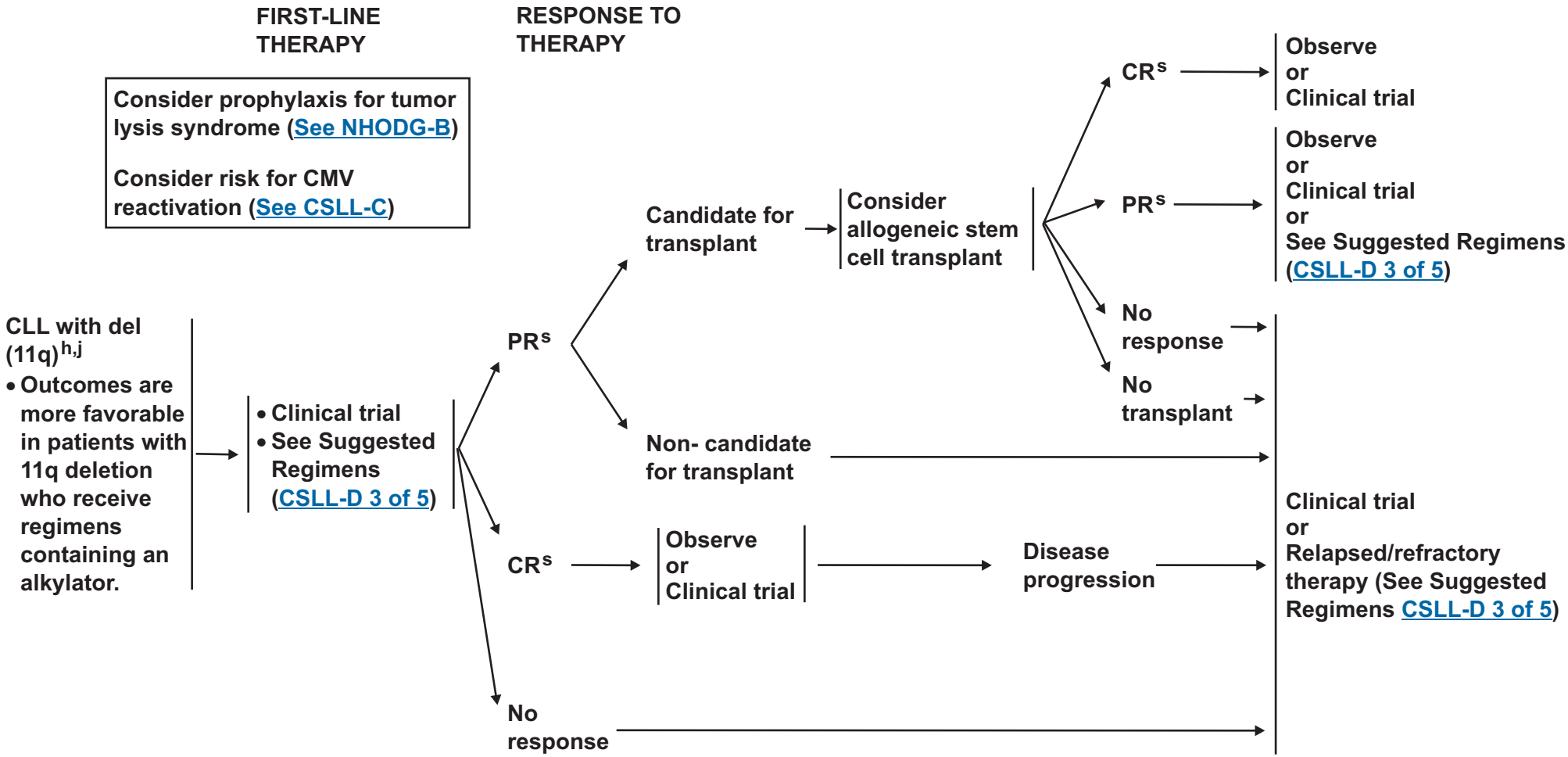


[h] See Supportive Care For Patients With CLL (CSLL-C).
[j] Absolute lymphocyte count alone is not an indication for treatment unless above 200- 300 x 10^9/L or symptoms related to leukostatsis.
[r] Patients with low positivity should be retested due to chance of false positive results.
[s] See Response Criteria: CLL (CSLL-E) or SLL (NHODG-C).

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CLL WITH DELETION OF 11q



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

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PROGNOSTIC INFORMATION FOR CLL[a]

Immunoglobulin Variable Region (IGHV) 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 anecdotal 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(1):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 present, others 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.
Autoimmune Cytopenias	• Auto-immume 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 thrombocytopenia purpura (ITP): Evaluate bone marrow for cause of low PLT • Pure red blood 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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SUGGESTED TREATMENT REGIMENS[a]
(in order of preference)
CLL without del (11q) or del (17p)

Frail patient, significant co-morbidity
(not able to tolerate purine analogs)

- Chlorambucil ± prednisone
- Rituximab (single)
- Pulse corticosteroids

First-line therapy[b]

- Age ≥ 70 y or younger patients with co-morbidities
  - Chlorambucil ± prednisone
  - BR (bendamustine, rituximab)[d]
  - Cyclophosphamide, prednisone ± rituximab
  - Alemtuzumab[c]
  - Rituximab
  - Fludarabine[e] ± rituximab
  - Cladribine
- Age < 70 y or older patients without significant co-morbidities
  - Chemoimmunotherapy[d]
    - FCR (fludarabine,[e] cyclophosphamide rituximab)
    - FR (fludarabine,[e] rituximab)
    - PCR (pentostatin, cyclophosphamide rituximab)
    - BR

Relapsed/Refractory therapy

- Long response > 3 y
  - Retreat as in first line therapy until short response
- Short response < 2 y for age ≥ 70 y
  - Chemoimmunotherapy[d]
    - Reduced-dose FCR[e]
    - Reduced-dose PCR
    - Bendamustine[d] ± rituximab
    - HDMP (high-dose methylprednisolone) + rituximab
  - Chlorambucil ± prednisone (if used first-line)
  - Ofatumumab
  - Alemtuzumab ± rituximab
  - Dose-dense rituximab (category 2B)
- Short response < 2 y for age < 70 y or older patients without significant co-morbidities
  - Chemoimmunotherapy[d]
    - FCR[e]
    - PCR[e]
    - BR
    - Fludarabine[e] + alemtuzumab
    - CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab
    - HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab
    - Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab
    - OFAR (oxaliplatin, fludarabine,[e] cytarabine, rituximab)
  - Ofatumumab
  - Alemtuzumab ± rituximab
  - HDMP + rituximab

See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)

See Suggested Regimens for CLL with del (17p) (2 of 5)

See Suggested Regimens for CLL with del (11q) (3 of 5)

[a] See references for regimens CSLL-D 4 of 5 and CSLL-D 5 of 5.
[b] Antibiotic prophylactic therapy for shingles and pneumocystis is recommended in purine analog-based and/or alemtuzumab combination therapy.
[c] Less effective for bulky (> 5 cm) lymphadenopathy; monitor for CMV reactivation.
[d] Monitor for myelosuppression.
[e] Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.

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SUGGESTED TREATMENT REGIMENS[a]
(in order of preference)
CLL with del (17p)

First-line therapy[b]

- FCR (fludarabine,[e] cyclophosphamide, rituximab)
- FR (fludarabine,[e] rituximab)
- HDMP (high-dose methylprednisolone) + rituximab
- Alemtuzumab[c] ± rituximab
- Bendamustine[d] + rituximab

Relapsed/Refractory therapy

- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab
- CFAR (cyclophosphamide, fludarabine,[e] alemtuzumab, rituximab)
- HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab
- OFAR (oxaliplatin, fludarabine,[e] cytarabine, rituximab)
- Ofatumumab[f]
- Alemtuzumab ± rituximab
- High-dose dexamethasone ± rituximab[g]
- Bendamustine[d] ± rituximab[g]

See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)

See Suggested Regimens for CLL without del (11q) or del (17p) (1 of 5)

See Suggested Regimens for CLL with del (11q) (3 of 5)

[a] See references for regimens CSLL-D 4 of 5 and CSLL-D 5 of 5.
[b] Antibiotic prophylactic therapy for shingles and pneumocystis is recommended in purine analog-based and/or alemtuzumab combination therapy.
[c] Less effective for bulky (> 5 cm) lymphadenopathy; monitor for CMV reactivation.
[d] Monitor for myelosuppression.
[e] Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.
[f] This is not effective in patients with lymph nodes > 5 cm.
[g] Rituximab should be added unless patient is known to be refractory to rituximab.

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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 co-morbidities
  - Chlorambucil ± prednisone
  - BR (bendamustine, rituximab)[d]
  - Cyclophosphamide, prednisone ± rituximab
  - Reduced-dose FCR (fludarabine,[e] cyclophosphamide, rituximab)
  - Alemtuzumab[c]
  - Rituximab
- Age < 70 y or older patients without significant co-morbidities
  - Chemoimmunotherapy[d]
    - FCR
    - BR
    - PCR (pentostatin, cyclophosphamide, rituximab)

See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)

See Suggested Regimens for CLL without del (11q) or del (17p) (1 of 5)

See Suggested Regimens for CLL with del (17p) (2 of 5)

Relapsed/Refractory therapy

- Long response > 3 y
  - Retreat as in first line therapy until short response
- Short response < 2 y for age ≥ 70 y
  - Chemoimmunotherapy[d]
    - Reduced-dose FCR[e]
    - Reduced-dose PCR
    - Bendamustine ± rituximab
    - HDMP (high-dose methylprednisolone) + rituximab
    - Chlorambucil ± prednisone (if used first line)
  - Ofatumumab
  - Alemtuzumab ± rituximab
  - Dose-dense rituximab (category 2B)
- Short response < 2 y for age < 70 y or older patients without significant co-morbidities
  - Chemoimmunotherapy[d]
    - FCR[e]
    - PCR[e]
    - BR
    - Fludarabine[e] + alemtuzumab
    - CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab
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    - OFAR (oxaliplatin, fludarabine,[e] cytarabine, rituximab)
  - Ofatumumab
  - Alemtuzumab ± rituximab
  - HDMP + rituximab

[a] See references for regimens CSLL-D 4 of 5 and CSLL-D 5 of 5.
[b] Antibiotic prophylactic therapy for shingles and pneumocystis is recommended in purine analog-based and/or alemtuzumab combination therapy.
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SUGGESTED TREATMENT REGIMENS
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Alemtuzumab
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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.
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Bendamustine + rituximab
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Chlorambucil
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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 + prednisone
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Cyclophosphamide, Fludarabine, Alemtuzumab, and Rituximab (CFAR)
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. Blood (ASH Annual Meeting Abstracts), 2007;110:Abstract 628.

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.

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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.
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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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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.
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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). 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(10):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]

Parameter	Complete response	Partial response	Progressive Disease	Stable Disease
Lymphadenopathy[b]	None above 1.0 cm	Decrease ≥ 50%	Increase ≥ 50%	Change from -49% to +49%
Liver and/or spleen size	Normal size	Decrease ≥ 50%	Increase ≥ 50%	Change from -49% to +49%
Constitutional symptoms	None	Any	Any	Any
Leukocytes	> 1500/mm^3	> 1500/mm^3 or > 50% improvement	Any	Any
Circulating B lymphocytes	Normal	Decrease ≥ 50% over baseline	Increase ≥ 50%	Change from -49% to +49%
Platelet count	> 100,000/mm^3	> 100,000/mm^3 or increase ≥ 50% over baseline	Decrease ≥ 50% over baseline	Change from -49% to +49%
Hemoglobin	> 11.0 g/dL (untransfused)	> 2 g/dL from baseline	Decrease of > 2 g/dL from baseline	Increase < 11.0 g/dL or < 50% over baseline, or decrease < 2 g/dL
Marrow	Normocellular, < 30% lymphocytes, no B-lymphoid nodules	Hypocellular, or ≥ 30% lymphocytes, or B-lymphoid nodules, or not done	Increase of lymphcytes to more than 30% from normal	No change of marrow infiltrate

[a] Eichhorst B and Hallek M. Revision of the guidelines for diagnosis and therapy of chronic lymphocytic leukemia (CLL). Best Practice & Research Clinical Haematology. 2007;20:469-477.

[b] Sum of the products of multiple lymph nodes (as evaluated by CT scans in clinical trials, or by physical exam or ultrasound in general practice).

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National Comprehensive Cancer Network®

NCCN Guidelines™ Version 1.2011
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 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[c,d]**
  - **Recommended panel for paraffin section immunohistochemistry: 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 genetic analysis to detect: antigen gene receptor rearrangements; BCL2 rearrangement**
- **Cytogenetics or FISH: t(14;18); t(8;14) or variants**
- **Paraffin section immunohistochemistry: Ki67[f]**

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**
- **Chest/abdominal/pelvic CT with contrast of diagnostic quality**
- **Hepatitis B testing[g]**
- **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 anthracenediones- based regimen is indicated**
- **Neck CT**
- **Beta-2-microglobulin**
- **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-2)**

Stage IIX, III, IV → **See Initial Therapy (FOLL-2)**

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

[e] In BCL2 negative young patients with localized disease, consider entity of pediatric follicular lymphoma.

[f] There are reports showing Ki67 proliferation fraction of > 30 % may be associated with a more aggressive clinical behavior but no evidence this should guide treatment decisions.

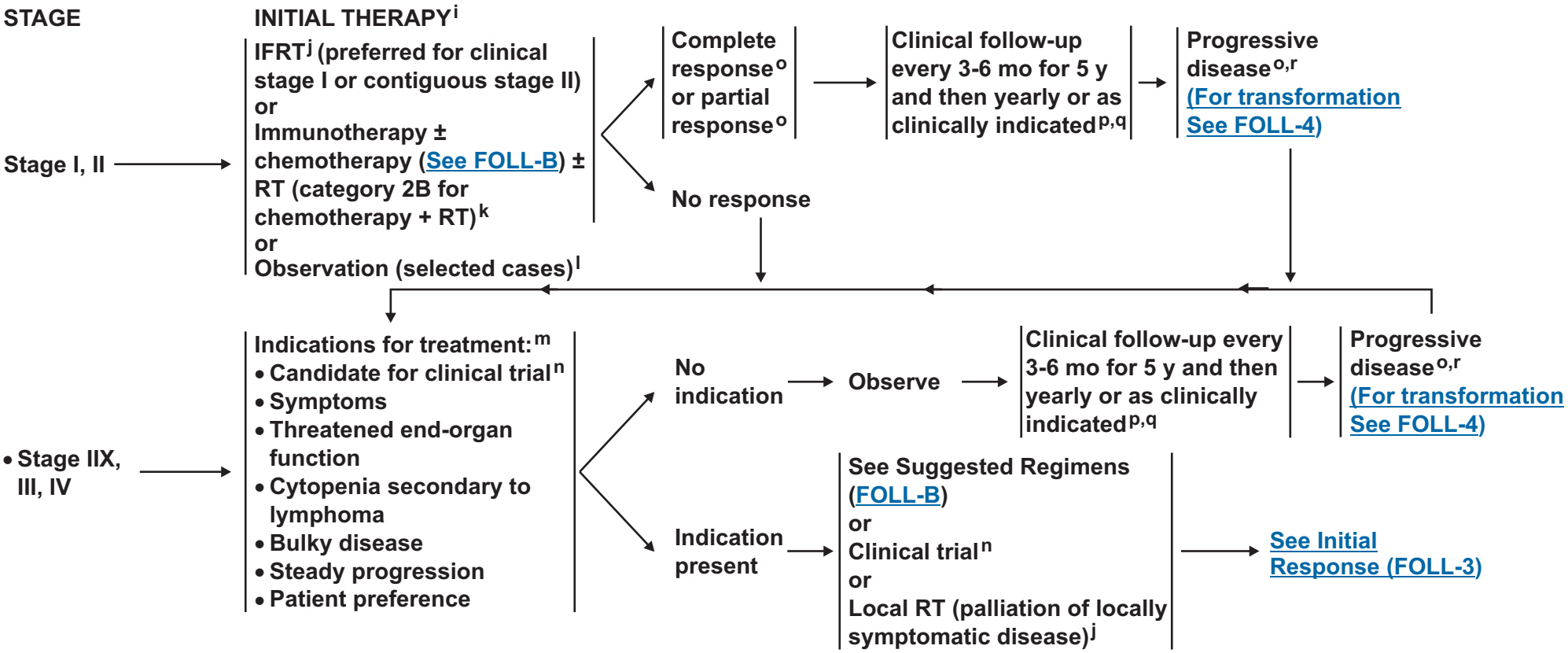
[g] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check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

[h] Bilateral or unilateral provided core biopsy is > 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.

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[i] When determining initial treatment, consider excluding profoundly myelotoxic regimens for patients who may be eligible for high dose therapy with autologous stem cell rescue.

[j] See Principles of Radiation Therapy (NHODG-E).

[k] 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.

[l] Observation may be appropriate in circumstances where toxicity of involved-field RT outweighs potential clinical benefit.

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

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

[o] See Response Criteria for Lymphoma (NHODG-C).

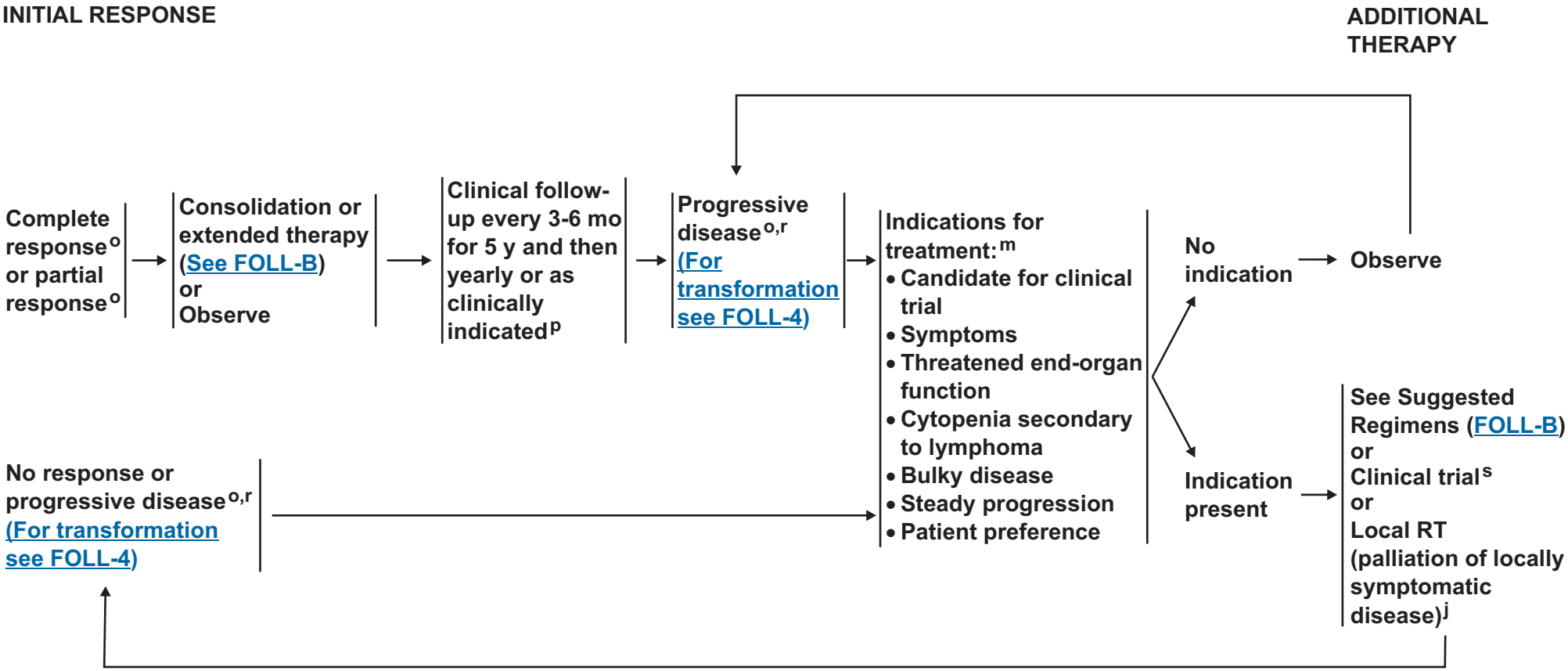
[p] Follow-up includes repeat diagnostic tests, including imaging (based on site of disease and clinical presentation) as clinically indicated.

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

[r] Progressive disease should be histologically documented to rule out transformation (preferentially, biopsy or marked increase in FDG uptake on PET), especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, new B symptoms develop, or there is marked heterogeneity or sites of intense FDG avidity on PET scan. A directed biopsy should be performed of a suspicious area. If transformation is histologically confirmed, treat with anthracycline-based therapy. Positive functional imaging does not replace biopsy to diagnose transformation. See Management of Transformation (FOLL-4).

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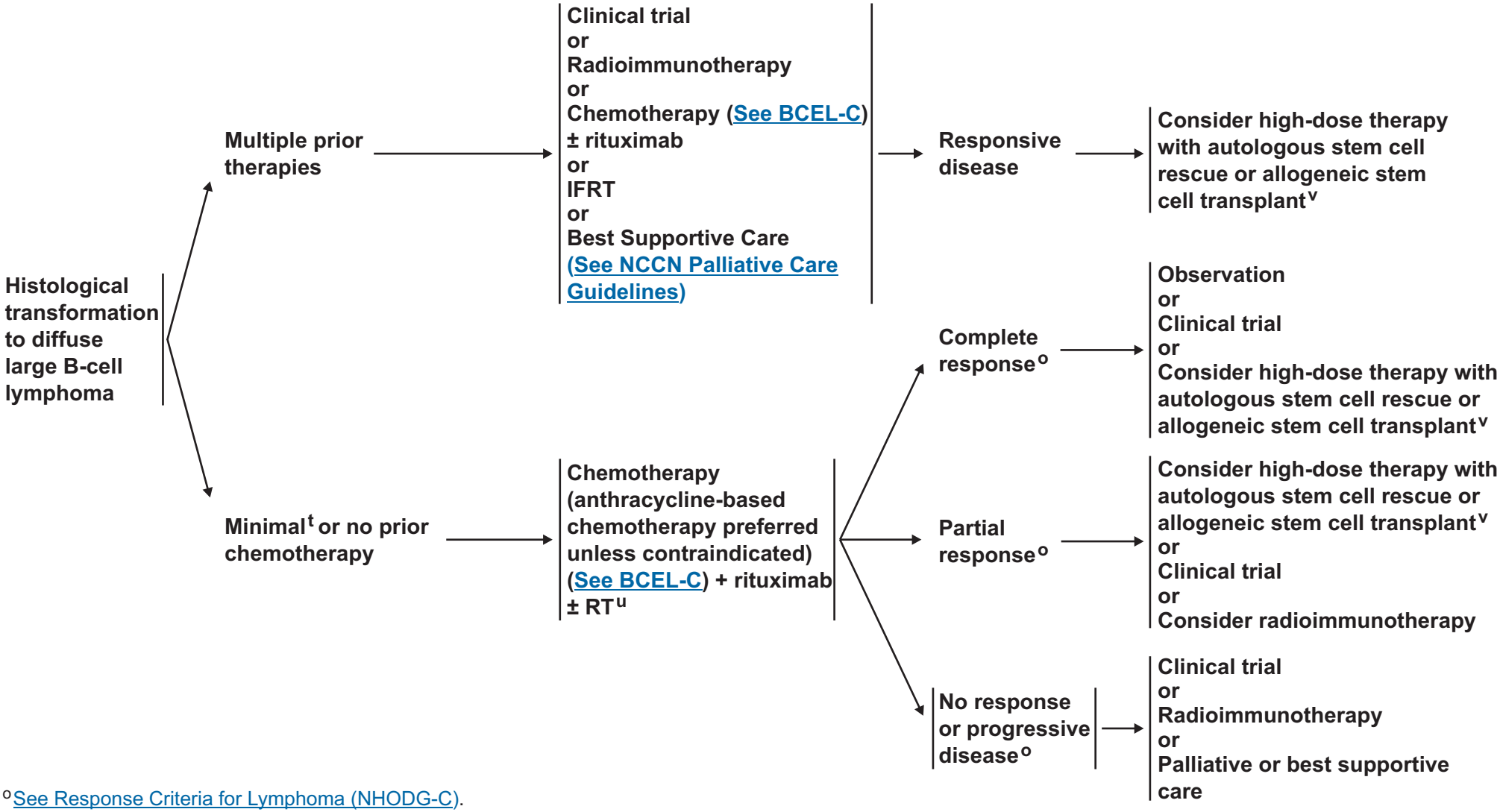
[j] See Principles of Radiation Therapy (NHODG-E).
[m] See GELF criteria (FOLL-A).
[o] See Response Criteria for Lymphoma (NHODG-C).
[p] Follow-up includes repeat diagnostic tests, including imaging (based on site of disease and clinical presentation) as clinically indicated (about every 6 mo).
[r] Progressive disease should be histologically documented to rule out transformation (preferentially, biopsy or marked increase in FDG uptake on PET), especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, new B symptoms develop, or there is marked heterogeneity or sites of intense FDG avidity on PET scan. A directed biopsy should be performed of a suspicious area. If transformation is histologically confirmed, treat with anthracycline-based therapy. Positive functional imaging does not replace biopsy to diagnose transformation. See Management of Transformation (FOLL-4).
[s] Clinical trials may involve novel agents, regimens, or transplantation.

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HISTOLOGICAL TRANSFORMATION TO DIFFUSE LARGE B-CELL LYMPHOMA



[o] See Response Criteria for Lymphoma (NHODG-C).
[t] Involved-field RT alone or one course of single agent therapy including rituximab.
[u] If locoregional transformation, consider adding RT.
[v] Strongly recommend this treatment be given in the context of a clinical trial; nonmyeloblative approaches may also be considered.

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NCCN Guidelines™ Version 1.2011
Follicular Lymphoma (grade 1-2)

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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)

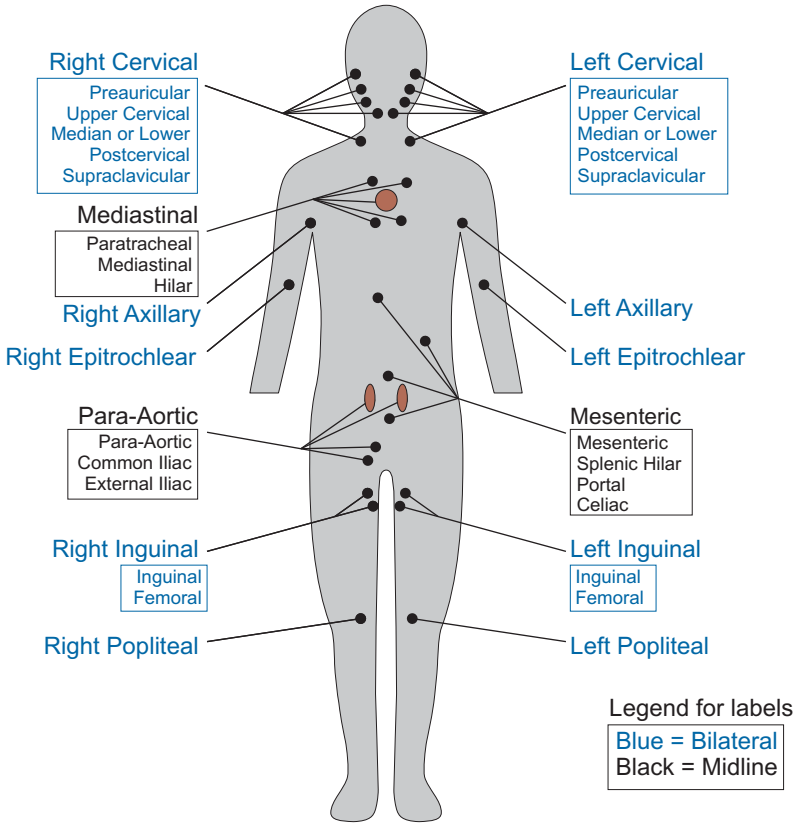
FLIPI - 1 CRITERIA[a,c]

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



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

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[a] This provides useful prognostic information which 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(7):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] The map is used to determine 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,d]
- Bendamustine + rituximab (category 1)
- RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)
- RCVP (rituximab, cyclophosphamide, vincristine, prednisone) (category 1)
- Fludarabine + rituximab
- RFND (rituximab, fludarabine, mitoxantrone, dexamethasone)
- Radioimmunotherapy[e,f] (category 2B)
- Rituximab

First-line Therapy for Elderly or Infirm (if none of the above are tolerable)
- Radioimmunotherapy
- Rituximab, preferred
- Single agent alkylators ± rituximab (eg, chlorambucil or cyclophosphamide)

First-line Consolidation or Extended Dosing
- Chemotherapy followed by radioimmunotherapy[e,f,g] (category 1)
- Rituximab maintenance[h] up to 2 y (category 1)

Second-line and Subsequent Therapy
- Chemoimmunotherapy (as in first-line therapy)
- FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab) (category 1)
- Radioimmunotherapy[e,f] (category 1)
- See Second-line Therapy for DLBCL (BCEL-C 1 of 3)[i]

Second-line Consolidation or Extended Dosing
- High dose therapy with autologous stem cell rescue[j]
- Allogeneic stem cell transplant for highly selected patients[k]
- Rituximab maintenance[h] (category 1)

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

See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)

[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] Initial management of patients with follicular lymphoma should include rituximab; use caution in patients with hepatitis B.

[e] 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.

[f] 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.

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

[h] In patients previously treated with chemotherapy, rituximab and anthracycline naive, maintenance rituximab extends disease-free, and event-free survival.

[i] These agents can be administered without restriction for transplantability.

[j] High dose therapy with autologous stem cell rescue is an appropriate consolidative therapy to patients in second or third remission.

[k] In highly selected patients, trials of fully ablative and nonmyeloablative allogeneic stem cell transplant have shown long term survival advantage, although there is a 2-year treatment-related mortality rate of approximately 25% for non-myeloablative and 40% for fully ablative.

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SUGGESTED TREATMENT REGIMENS
References

First-line therapy

Bendamustine + rituximab:
Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab is superior in respect of progressionfree survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: Final results of a randomized phase III study of the StiL (Study Group Indolent Lymphomas, Germany). Blood (Blood) 2009;114:405.

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.

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab
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.

CVP (cyclophosphamide, vincristine, prednisone) + rituximab
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.

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.

FND (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.

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
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.
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. Blood 2009;114:3759.

First-line Consolidation or Extended Dosing

Chemotherapy followed by radioimmunotherapy
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.
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.

Chemotherapy followed by rituximab
Salles GA, Seymour JF, Feugier P, et al. Rituximab maintenance for 2 years in patients with untreated high tumor burden follicular lymphoma after response to immunochemotherapy. J Clin Oncol (Meeting Abstracts) 2010;28:8004.

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SUGGESTED TREATMENT REGIMENS
References

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.

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(2):204-210.

Kahl BS, Bartlett NL, Leonard JP, et al. Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma. Cancer 2010;116:106-114.

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.

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.

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;19:3918-3928.

Fisher RI, Kaminski MS, Wahl RL, et al. Tositumomab and iodine-131 tositumomab produces durable complete remissions in a subset of heavily pretreated patients with low-grade and transformed non-Hodgkin's lymphomas. J Clin Oncol 2005;23:7565-7573.

Second-line 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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NCCN Guidelines™ Version 1.2011
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** → See Diagnosis and Workup (NGMLT-1)

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

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

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.[a,b]
- Diagnosis of Gastric MALT lymphoma requires an endoscopic biopsy and an FNA is never adequate.
- Adequate immunophenotyping to establish diagnosis[c,d]
  - Recommended panel for paraffin section immunohistochemistry: 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 stain (gastric), if positive, then PCR or FISH for t(11;18)[e]

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Molecular genetic analysis to detect: antigen receptor gene rearrangements
- Cytogenetics or FISH: t(1;14), t(14;18), t(3;14)

→

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[f] if rituximab contemplated
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Endoscopy with ultrasound (if available) with multiple biopsies of anatomical sites
- 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 anthracenediones- based regimen is indicated
- Hepatitis C testing
- Discussion of fertility issues and sperm banking
- SPEP

→ See Initial Therapy (MALT-2)

[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 Diffuse Large B-Cell Lymphoma Guidelines (BCEL-1).
[c] Typical immunophenotype: CD10-, CD5-, CD20+, cyclin D1-, BCL2 follicles-.
[d] See Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms (NHODG-A).
[e] Locally advanced disease is more likely in patients with gastric MALT lymphoma with t(11;18).
[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.

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STAGE[g]	INITIAL THERAPY		
Stage I_{E1}, H. pylori positive	→	Currently accepted antibiotic therapy for H. pylori[i]	→ Evaluate for H. pylori eradication with endoscopy (MALT-3)
Stage I_{E2}[h] or Stage II_E[h] H. pylori positive	→	Currently accepted antibiotic therapy for H. pylori[i]	→ Evaluate for H. pylori eradication with endoscopy (MALT-3)
Stage I_E or II_E H. pylori negative	→	RT[j,k] (preferred) or Rituximab (if RT is contraindicated)	→ Endoscopy for restaging, as per MALT-4
Stage III_E/IV (advanced-stage disease uncommon)	→	Indications for treatment: • Candidate for clinical trial[l] • Symptoms • GI bleeding • Threatened end-organ function • Bulky disease • Steady progression • Patient preference	No indication → Observe
			Indication present[m] → Induction chemo-immunotherapy[n] or Locoregional RT in specific settings[k] → Endoscopy for restaging, if evidence of recurrence, manage per follicular lymphoma (see FOLL-3)

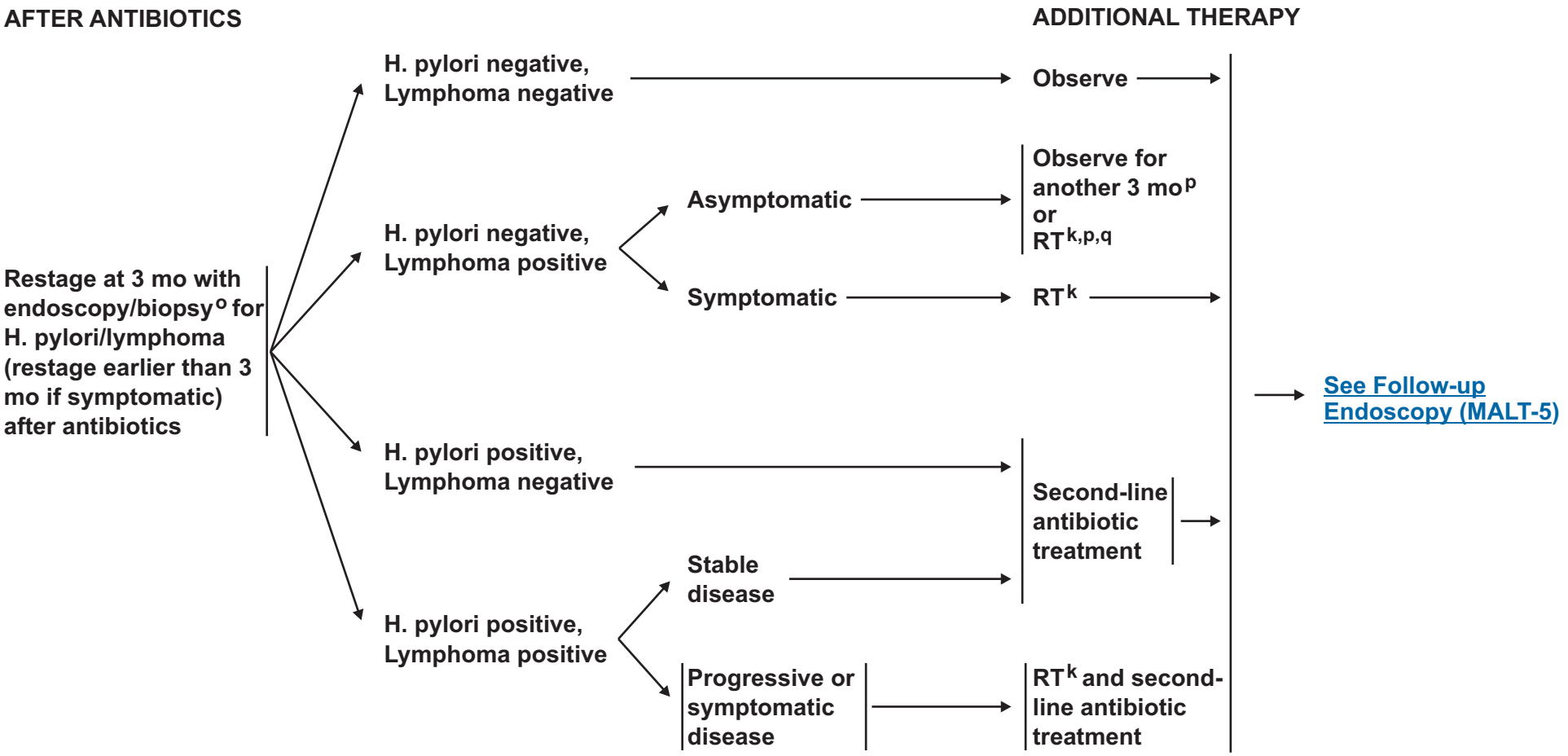
[g] See Lugano Staging System for gastrointestinal lymphoma (MALT-A).
[h] Involvement of submucosa or regional lymph nodes are much less likely to respond to antibiotic therapy. If there is persistent disease after evaluation, RT may be considered earlier in the course.
[i] t(11;18) is a predictor for lack of response to antibiotics. These patients should be considered for alternative therapy.
[j] If negative by both histology and serum antibodies, RT recommended.
[k] See Principles of Radiation Therapy (NHODG-E).
[l] Given incurability with conventional therapy, consider investigational therapy as first line of treatment.
[m] Surgical resection is generally limited to specific clinical situations, ie, life-threatening hemorrhage.
[n] See Suggested Treatment Regimens (FOLL-B).

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3-MONTH RESTAGING AND FOLLOW-UP ENDOSCOPY



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

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

[p] 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).

[q] If patient originally had clinical Stage I_{E2} or Stage II_{E}, early RT should be considered if there is no response to antibiotics.

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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[o] after RT	H. pylori negative Lymphoma negative	Observe	See Follow-up Endoscopy (MALT-5)
	H. pylori negative Lymphoma positive	See FOLL-2	
	H. pylori positive Lymphoma negative	Consider antibiotic treatment	See Follow-up Endoscopy (MALT-5)
	H. pylori positive Lymphoma positive	See FOLL-2	

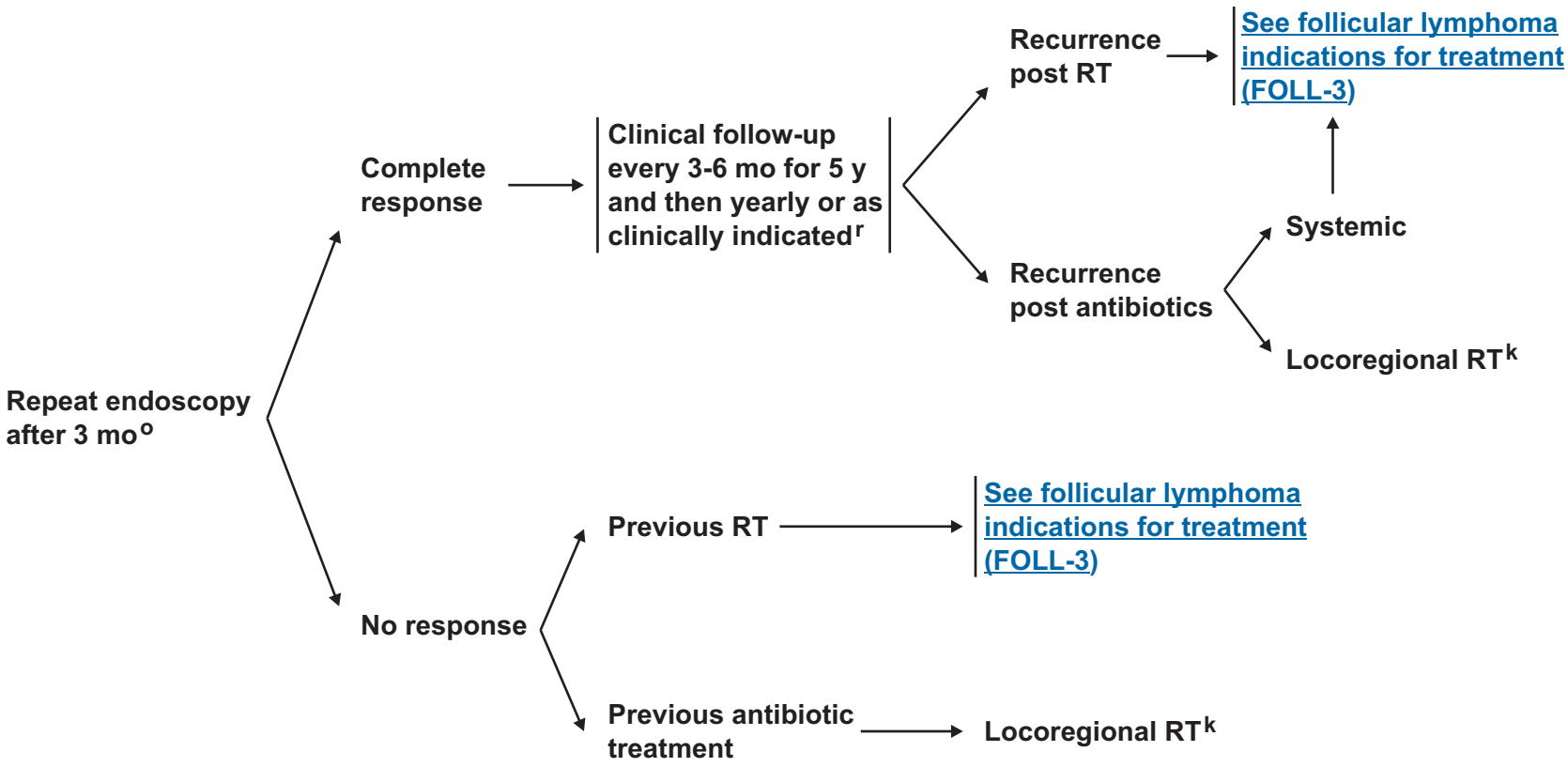
[o]Biopsy to rule out large cell lymphoma. Any area of DLBCL should be treated according to the Diffuse Large B-Cell Lymphoma Guidelines (BCEL-1).

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FOLLOW-UP ENDOSCOPY



[k] See Principles of Radiation Therapy (NHODG-E).
[o] Biopsy to rule out large cell lymphoma. Any area of DLBCL should be treated according to the Diffuse Large B-Cell Lymphoma Guidelines (BCEL-1).
[r] Optimal interval for follow-up endoscopy and imaging is not known. Follow-up endoscopy and imaging at NCCN institutions is driven by symptoms.

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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 III-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 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.

[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 MZL or like disseminated FL.

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Extranodal Marginal Zone B-Cell Lymphoma[a]

Nongastric MALT Lymphoma[b]

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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.
- Adequate immunophenotyping to establish diagnosis[c,d]
  - Recommended panel for paraffin section immunohistochemistry: 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 genetic analysis to detect: antigen receptor gene rearrangements; PCR for t(11;18)
- Cytogenetics or FISH: t(11;18); t(11;14); t(3;14); 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 anthracenediones- based regimen is indicated
- Bone marrow biopsy ± aspirate (for patients with multifocal disease)
- Endoscopy with multiple biopsies of anatomical sites
- PET-CT scan
- MRI
- Hepatitis C testing
- Discussion of fertility issues and sperm banking
- SPEP

→ See Initial Therapy (NGMLT-2)

[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 adenxa, 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] Non-cutaneous, for cutaneous marginal zone B-cell lymphoma, see CUTB.

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

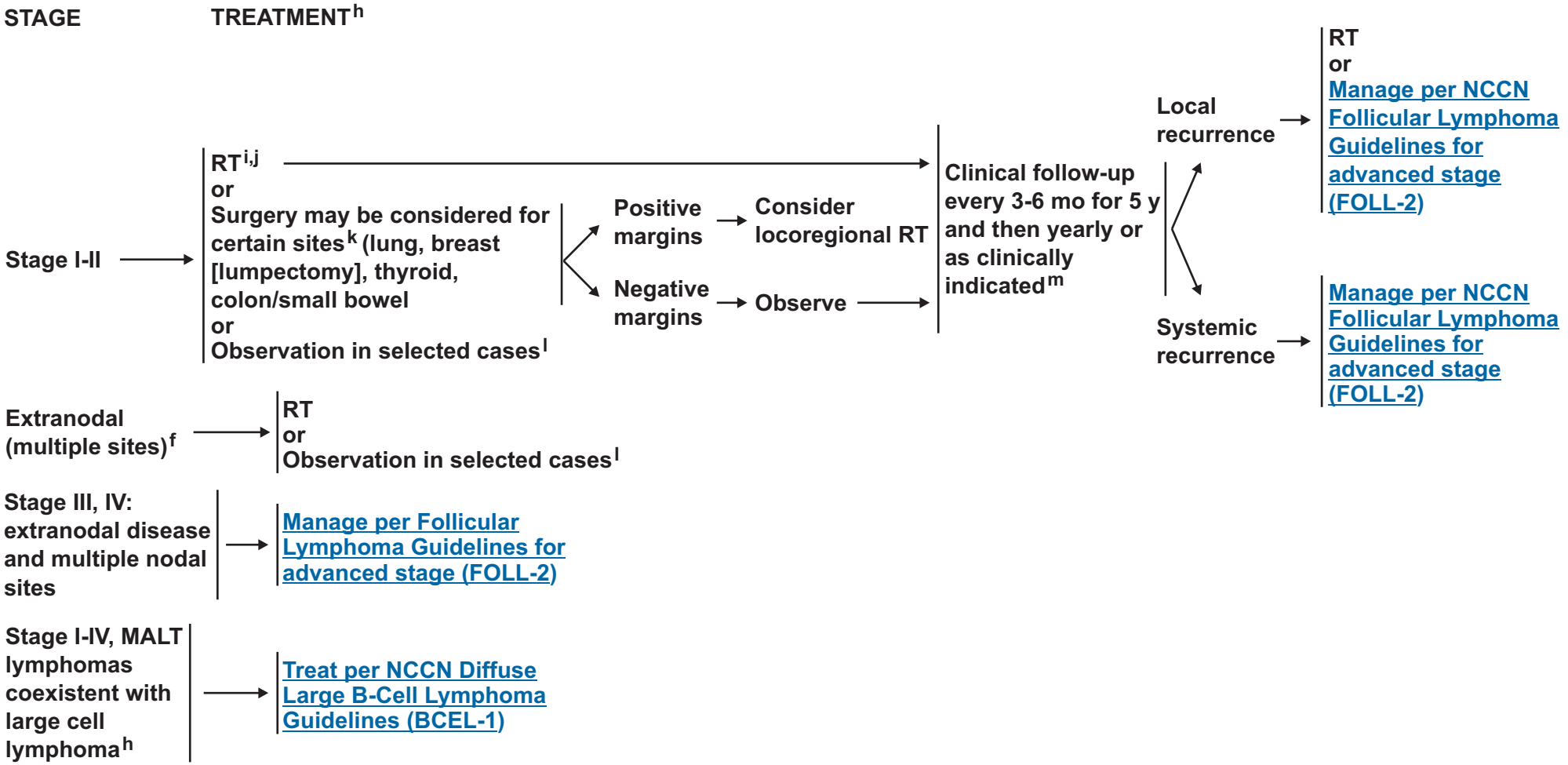
[d] See Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms (NHODG-A).

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

[g] DLBCL coexistent with MALT cell lymphoma is managed as DLBCL.

[h] 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.

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

[j] See Principles of Radiation Therapy (NHODG-E).

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

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

[m] Follow-up includes diagnostic tests and imaging as clinically 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]**
  - **Paraffin 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 genetic analysis to detect: antigen receptor gene rearrangements; PCR for t(11;18)**
- **Cytogenetics or FISH: t(11;18); t(1;14); t(14;18); del(13q); del(7q)**

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 anthracenediones-based regimen is indicated**
- **Additional imaging as appropriate**
- **PET-CT scan**
- **Hepatitis C testing**
- **Discussion of fertility issues and sperm banking**
- **SPEP**

→ **See Management as per Follicular Lymphoma (FOLL-2)**

[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 and Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-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.

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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]**
  - **Recommended panel for paraffin section immunohistochemistry: CD20, CD3, CD5, CD10, BCL2, kappa/lambda, CD21 or CD23, cyclin D1, IgD, CD43, annexin-1**
    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 genetic analysis to detect: antigen receptor gene rearrangements; PCR for t(11;18)**
- **Cytogenetics or FISH: CLL panel; t(11;18); t(11;14); t(14;18); del(7q)**

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**
- **Directs Coombs testing**

See Initial Therapy (SPLN-2)

[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.

[b] Typical immunophenotype: CD10-, CD5-, CD20+, CD23-/+, CD43-/+ and cyclin D1-, BCL2 follicles-, annexin-1, CD103- (distinction from hairy cell leukemia) with expression of both IgM and IgD.

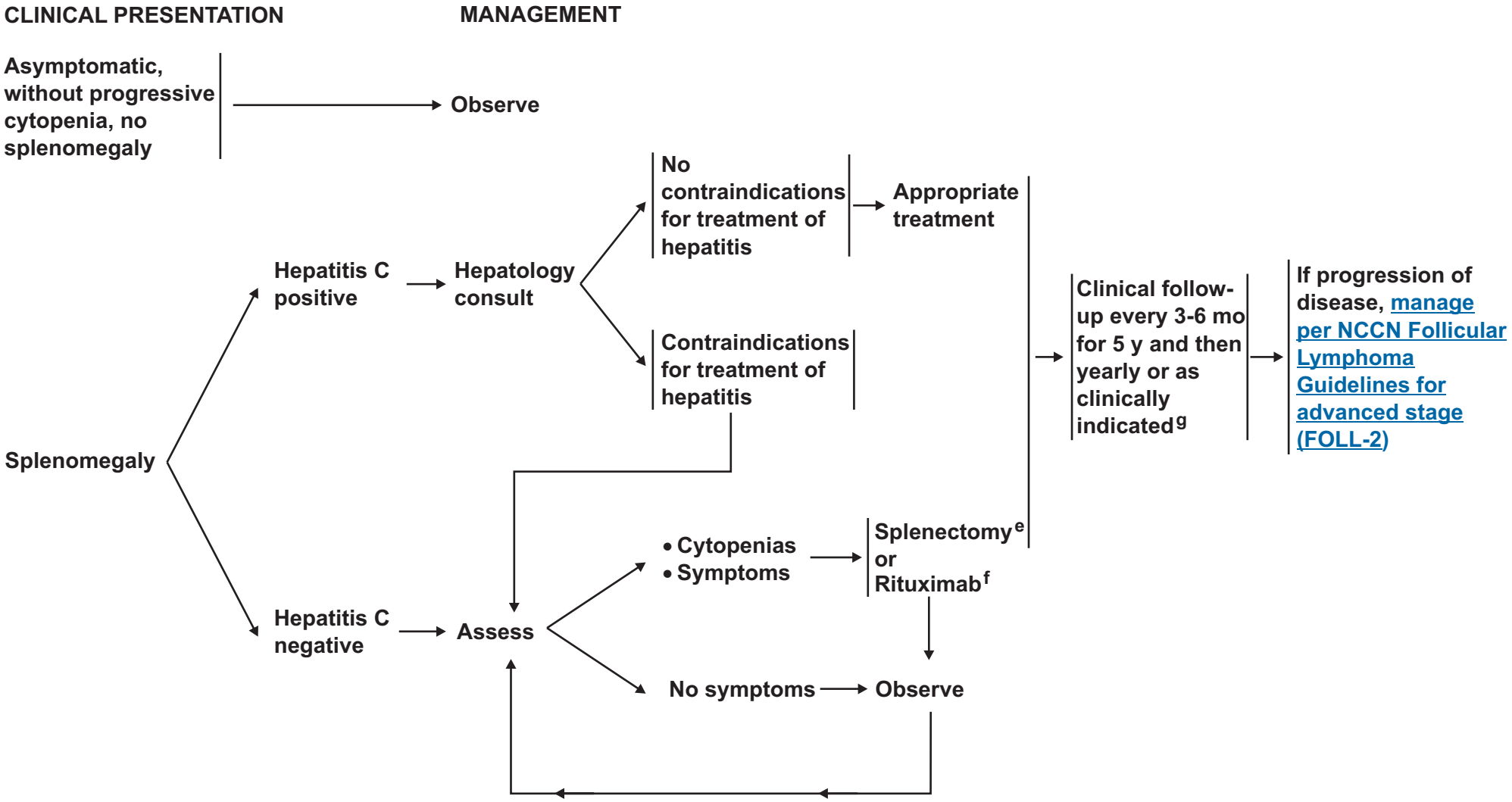
[c] See Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms (NHODG-A).

[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.

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[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.

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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]**
  - **Recommended panel for paraffin section immunohistochemistry: CD20, CD3, CD5, cyclin D1, CD10, CD21, CD23, BCL2, BCL6, Ki67[c]**
    or
  - **Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **Molecular genetic analysis to detect: antigen receptor gene rearrangements; BCL1 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 anthracenediones- 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)**

[a] Typical immunophenotype: CD5+, CD20+, CD43+, CD23-/+, cyclin D1+, CD10-/+ Note: Some cases of MCL may be CD5- or CD 23+. If the diagnosis is suspected, cyclin D1 staining or FISH for t(11;14) should be done.

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

[c] Ki67 proliferation fraction of < 30% is associated with a more favorable prognosis. However, it is not used to guide treatment.

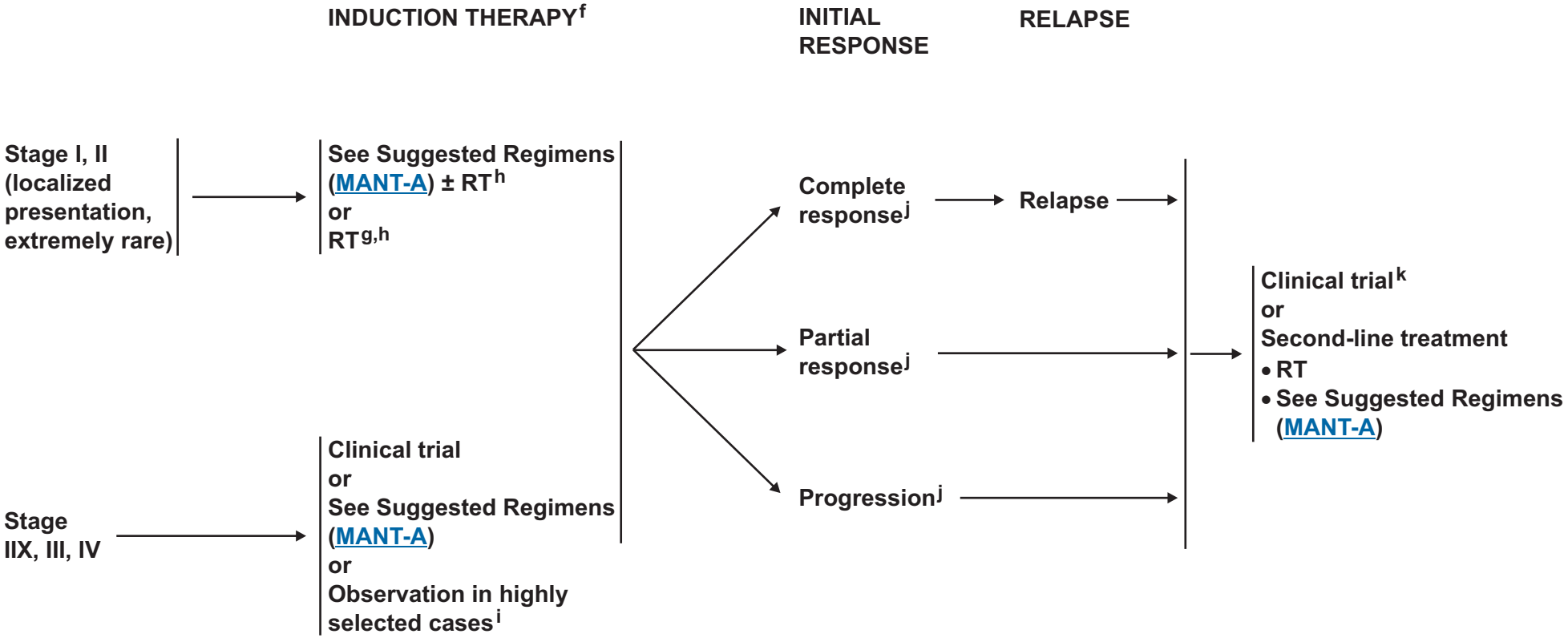
[d] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check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

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

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[f]Early referral for high dose therapy with stem cell rescue is advisable for planning purposes.
[g]Leitch HA, Gascoyne RD, Chhanabhai M, et al. Limited-stage mantle-cell lymphoma. Ann Oncol 2003;14:1555-1561.
[h]See Principles of Radiation Therapy (NHODG-E).
[i]Martin P, Chadburn A, Christos P, et al. Outcome of deferred initial therapy in mantle-cell lymphoma. J Clin Oncol 2009;27:1209-1213.
[j]See Response Criteria for Lymphoma (NHODG-C).
[k]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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SUGGESTED TREATMENT REGIMENS[a]
(in alphabetical order)

InductionTherapy[b]

- **Aggressive therapy**
  - **HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab**
  - **NORDIC regimen (dose-intensified induction immunochemotherapy with rituximab + cyclophosphamide, vincristine, doxorubicin, prednisone [maxi-CHOP]) alternating with rituximab + high-dose cytarabine)**
  - **CALGB regimen (rituximab + methotrexate with augmented CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone])**
  - **Sequential RCHOP/RICE (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (rituximab,ifosfamide, carboplatin, etoposide)**
- **Less aggressive therapy**
  - **Bendamustine ± rituximab**
  - **CHOP ± rituximab[c]**
  - **Cladribine + rituximab**
  - **CVP (cyclophosphamide, vincristine, prednisone) ± rituximab**
  - **Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + 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)**
- **Lenalidomide ± rituximab**
- **PCR (pentostatin, cyclophosphamide, rituximab)**
- **PEPC (prednisone, etoposide, procarbazine, cyclophosphamide) ± rituximab**
- **See Second-line Therapy for DLBCL (BCEL-C 1 of 3)[f]**

Second-line Consolidation

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

See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)

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

[b] There are no prospective randomized comparative trials with induction therapy regimens for mantle cell lymphoma.

[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] These agents can be administered without restriction for transplantability.

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SUGGESTED TREATMENT REGIMENS
References

InductionTherapy

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.

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 (rituximab + methotrexate with augmented CHOP):

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;21:133-9.

Less aggressive therapy

Bendamustine + rituximab

Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab Is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: Final results of a randomized phase III study of the StiL (Study Group Indolent Lymphomas, Germany). Blood (ASH Annual Meeting Abstracts). 2009;114:405.

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.

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.

CVP with or without rituximab

Teodorovic I, Pittaluga S, Kluin-Nelemans J, 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.

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.

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

Wilson WH, Gutierrez M, O'Connor P, et al. The role of rituximab and chemotherapy in aggressive B-cell lymphoma: a preliminary report of dose-adjusted EPOCH-R. Semin Oncol 2002;29:41-47.

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 Oncology 2006;17:1418-1423.

First-line consolidation

High dose therapy with autologous stem sell 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. Annals of Hematology 2007;86:101-105.

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SUGGESTED TREATMENT REGIMENS
References

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.

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 cyclophosphamid) ± 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. ASH Annual Meeting Abstracts. 2005;106:945.

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.

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). ASCO Meeting Abstracts. 2009;27:8569.

Lenalidomide + rituximab

Wang L, Fayad L, Hagemeister FB, et al. A phase I/II study of lenalidomide in combination with rituximab in relapsed/refractory mantle cell lymphoma. ASH Annual Meeting Abstracts. 2009;114:2719.

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(10):2228-2232.

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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]**
  - **Recommended panel for paraffin section immunohistochemistry: CD20, CD3, CD5, CD10, CD45, BCL2, BCL6, Ki-67, IRF4/MUM1**
    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**
  - **Paraffin panel: cyclin D1, kappa/lambda, CD138, EBV, ALK, HTLV**
- **Molecular genetic analysis to detect: antigen receptor gene rearrangements; BCL1, BCL2, MYC rearrangements[e]**
- **Cytogenetics or FISH: t(14;18);[e] t(3;v); t(8;14)**

SUBTYPES

- **Subtypes included:**
  - **Diffuse large B-cell lymphoma (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:**
  - **Cutaneous B-cell lymphoma (See CUTB-1)**
  - **Primary DLBCL of the CNS**

Primary Mediastinal Large B-Cell Lymphoma (PMBL), see BCEL-B.

[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.

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

[c] Typical immunophenotype: CD20+, CD45+, CD3-; other markers used for subclassification.

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

[e] Standard of care is not established for DLBCL with t(14;18) with concurrent MYC rearrangements.

[f] Germinal center (or follicular center) cell phenotype is not equivalent to follicular lymphoma and can occur in DLBCL and Burkitt lymphoma. Morphology is required to establish diagnosis.

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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
- Unilateral or bilateral bone marrow biopsy (1-2 cm) ± aspirate
- Calculation of International Prognostic Index (IPI)[b]
- Hepatitis B testing[g]
- MUGA scan/echocardiogram if anthracycline or anthracenediones- based regimen is indicated
- PET-CT scan
- 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

→ See Induction Therapy (BCEL-3)

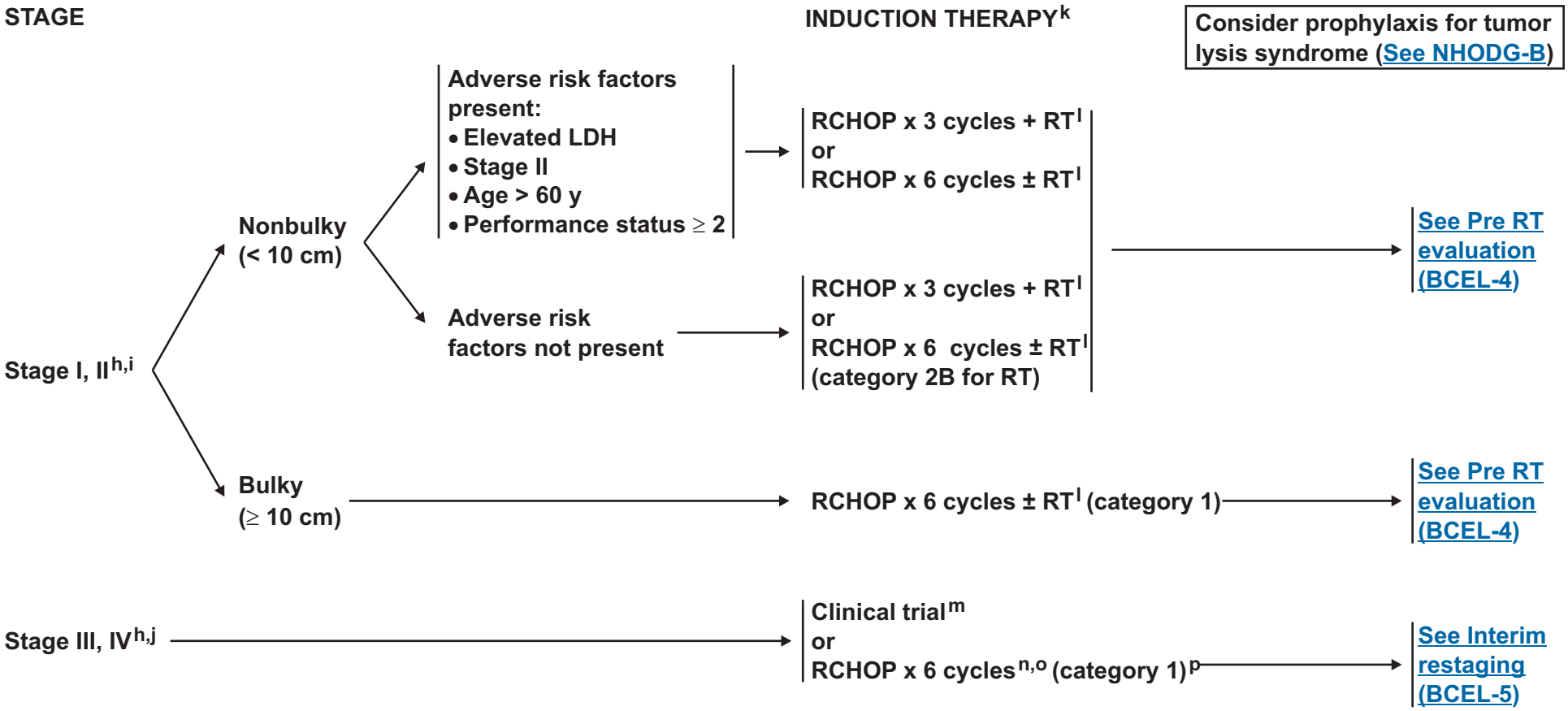
[b] See International Prognostic Index (BCEL-A).

[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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[h] In testicular lymphoma, after completion of chemotherapy, RT should be given to contralateral testis (30-36 Gy).

[i] In patients who are not candidates for chemotherapy involved field radiation therapy (IFRT) is recommended.

[j] In selected settings (paranasal sinus, testicular, epidural, bone marrow with large cell lymphoma, HIV lymphoma, or ≥ 2 extranodal sites), CNS prophylaxis should be given (4-8 doses of intrathecal methotrexate and/or cytarabine during the course of treatment). Recent data regarding Stage IE DLBCL of breast has been suggested as a potential risk for CNS disease.

[k] Recommendations are for HIV-negative lymphoma only. See AIDS-2 for HIV-positive DLBCL.

[l] See Principles of Radiation Therapy (NHODG-E).

[m] May include high-dose therapy.

[n] Based on current clinical trials, CHOP is preferable due to reduced toxicities, but other comparable anthracycline-based regimens are acceptable.

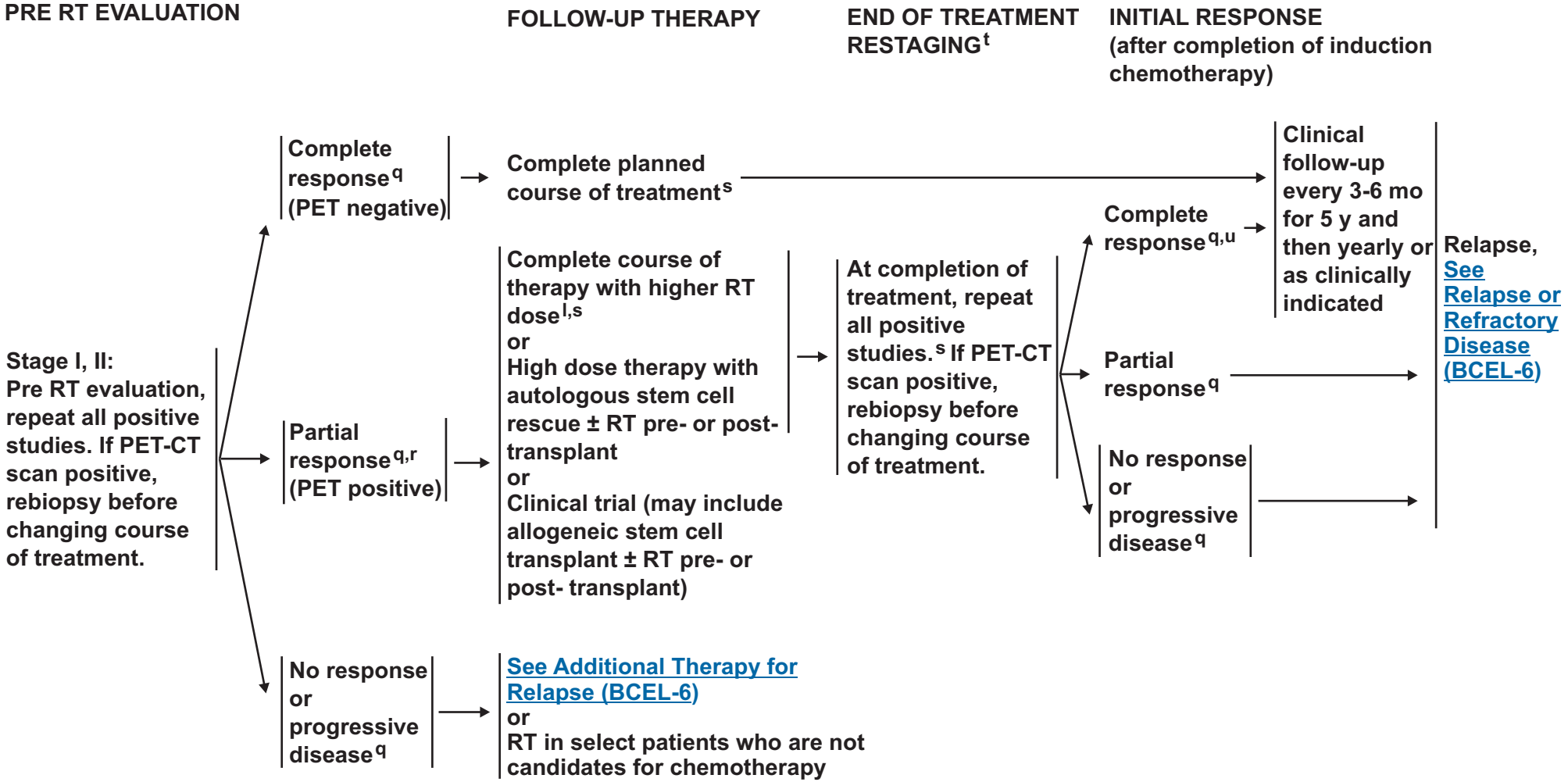
[o] For other regimens, see BCEL-C.

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

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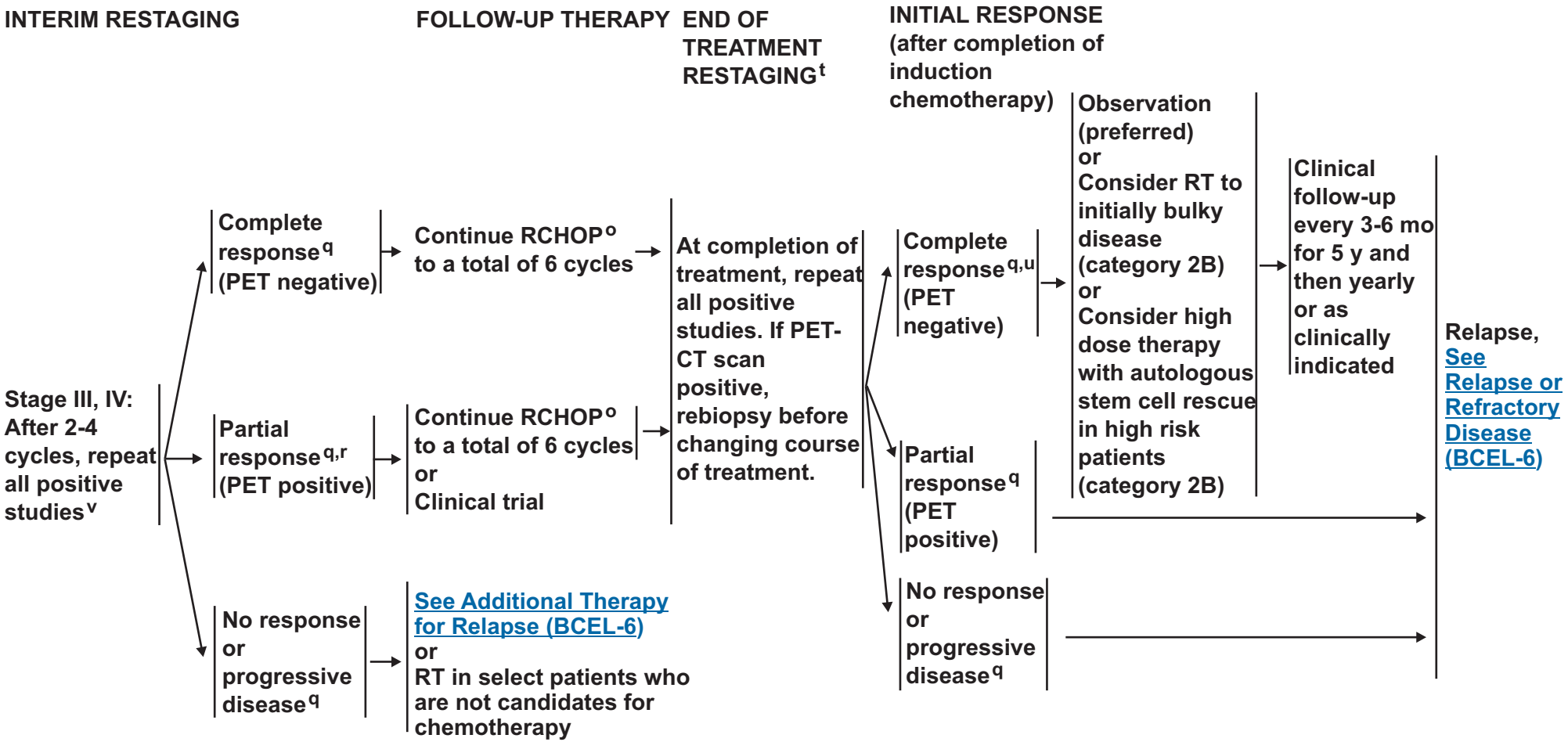
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[l] See Principles of Radiation Therapy (NHODG-E).
[q] See Response Criteria for Lymphoma (NHODG-C).
[r] Documented PR includes a biological measure of disease: positive PET-CT scan, or ideally positive biopsy.
[s] Wait a minimum of 8 weeks after RT to repeat PET-CT scan. The optimum timing of repeat PET-CT is unknown. False positives may occur due to posttreatment changes.
[t] There is evidence that addition of maintenance rituximab does not improve survival.
[u] Patients in first remission may be candidates for consolidation trials including high dose therapy with autologous stem cell rescue.

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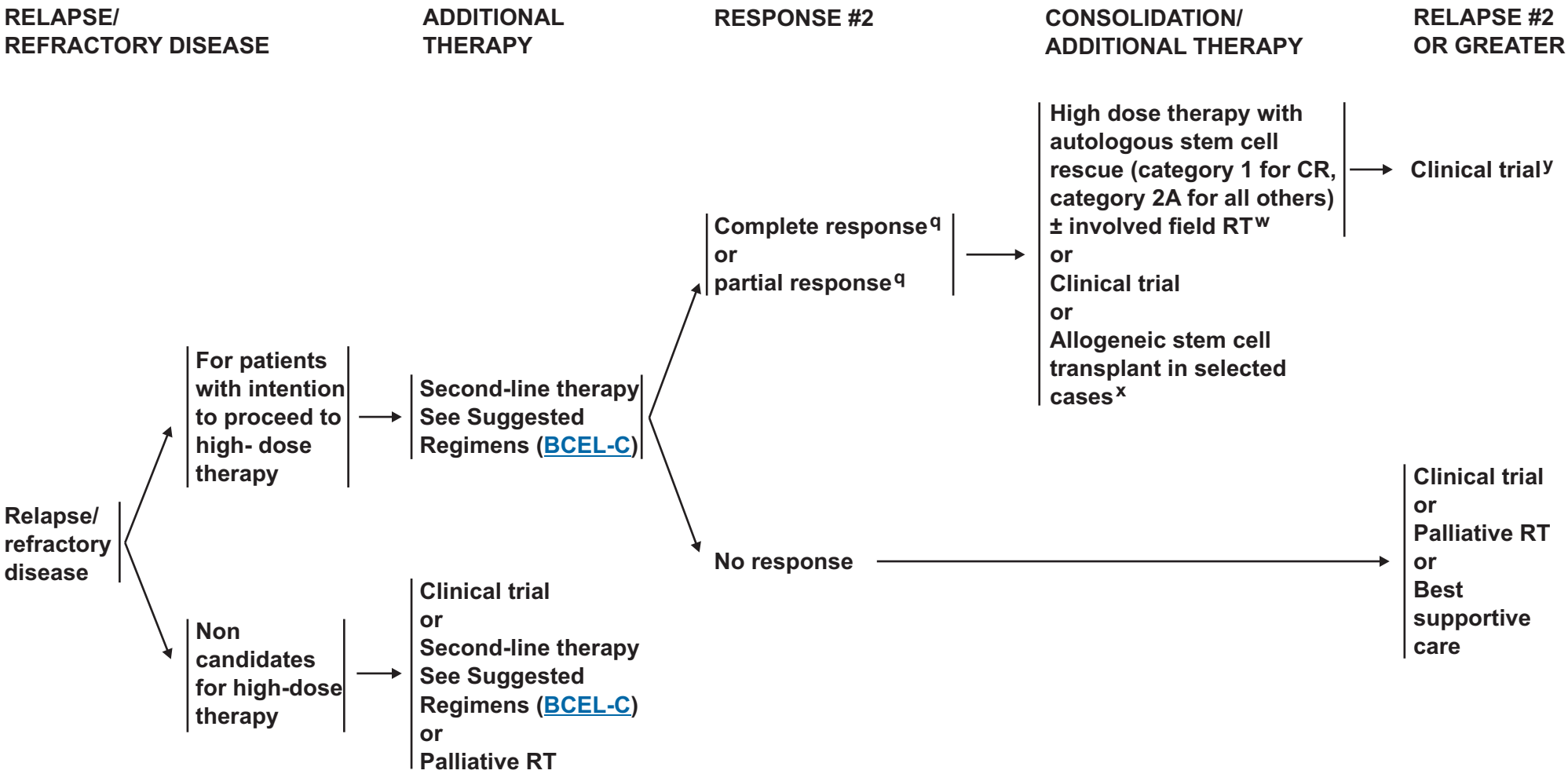
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[o]For other regimens, see BCEL-C.
[q]See Response Criteria for Lymphoma (NHODG-C).
[r]Documented PR includes a biological measure of disease: positive PET-CT scan, or ideally positive biopsy.
[t]There is evidence that the addition of maintenance rituximab does not improve survival.
[u]Patients in first remission may be candidates for consolidation trials including high dose therapy with autologous stem cell rescue.
[v]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.

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[q] See Response Criteria for Lymphoma (NHODG-C).

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

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

[y] 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.

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INTERNATIONAL PROGNOSTIC INDEX[a]

ALL PATIENTS:
- Age > 60 years
- Serum LDH > 1 x 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 > 1 x normal
- Performance status 2-4

INTERNATIONAL INDEX, PATIENTS ≤ 60 YEARS:

• Low	0
• Low/intermediate	1
• High/intermediate	2
• High	3

[a] Adapted with permission, The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-hodgkin's lymphoma. N Engl J Med1993; 329:987-994. Copyright © 1993 Massachusetts Medical Society. All rights reserved.

Back to Workup (BCEL-1)

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Primary Mediastinal Large B-Cell Lymphoma (PMBL)

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.

- **Clinical pathologic correlation is required to establish diagnosis.**
- **Optimal first-line therapy is more controversial than other subtypes of NHL.**
- **Because of relative rarity of PMBL, the role of R-CHOP-21 is not established as the definitive treatment option for this disease. However, R-CHOP-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.**
- **Role of RT is controversial; if PET-CT scan negative at the end of treatment, may be observed.**
- **Residual mediastinal masses are common. PET-CT scan is essential post-treatment. Biopsy of PET- CT scan positive mass is recommended if additional treatment is contemplated.**

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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 2B)
- Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + ritiximab (category 2B)

First-line Therapy for patients with poor left ventricular function[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)

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

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
- 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)
- Clinical trial
- CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) ± rituximab - PO and IV
- DA-EPOCH ± rituximab
- CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± rituximab
- GDP ± rituximab
- GemOx ± rituximab
- Lenalidomide ± rituximab
- Rituximab

See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)

[a] See references for regimens BCEL-C 2 of 3 and BCEL-C 3 of 3.

[b] Inclusion of any anthracycline or anthracenedione in patients with impaired cardiac functioning should have more frequent cardiac monitoring.

[c] There is limited published data regarding the use of these regimens, however, they are used at NCCN institutions for the first-line treatment of DLBCL for patients with poor ventricular left function.

[d] If upward dose adjustment is necessary, doxorubicin should be maintained at base dose and not increased.

[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] Rituixmab would be included in second line therapy if there is relapse after a reasonable remission (> 6 mo); however, rituximab would often be omitted in patients with primary refractory disease.

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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;26:2258-226.

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.

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.

Dose-dense CHOP 14 + rituximab

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

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. ASH Annual Meeting Abstracts. 2009;114:2701-.

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.

First-line Therapy for patients with poor ventricular left 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 (ritximab, cyclophosphamide, etoposide, vincristine, prednisone)

Moccia 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. 2009 ASH Annual Meeting. Abstract 408.

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SUGGESTED TREATMENT REGIMENS
References

Second-line Therapy

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. R-ICE versus R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by autologous stem cell transplantation: CORAL study. J Clin Oncol 2009;27:8509-.

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.

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(2):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.

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:i17-20.

Gisselbrecht C, Glass B, Mounier N, et al. R-ICE versus R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by autologous stem cell transplantation: CORAL study. J Clin Oncol 2009;27:8509-.

Lenalidomide

Czuczman MS, Vose J, Zinzani P, et al. Efficacy and safety of lenalidomide oral monotherapy in patients with relapsed or refractory diffuse large B-cell lymphoma: Results from an international study (NHL-003). J Clin Oncol (Meeting Abstracts). 2009;27:e19504.

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.

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]**
  - **Paraffin 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 or FISH: t(8;14) or variants; MYC; IgH; BCL2; BCL6 rearrangements**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **ISH for EBV EBER**
- **Molecular genetic analysis to detect: antigen receptor gene rearrangements; MYC rearrangement**

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**
- **Hepatitis B testing[e]**
- **MUGA scan/echocardiogram if anthracycline or anthracenediones- 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**
- **Beta-2-microglobulin**
- **PET-CT scan[f]**

→ **See Risk Assessment and Induction Therapy (BURK-2)**

[a] WHO 2008 classification recognizes that it may not always be possible to distinguish between DLBLC and Burkitt lymphoma. In the setting where it is not possible to distinguish, aggressive therapy per this guideline is appropriate in selected cases.

[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-, Ki67+ (100%), BCL2-, BCL6+, MYC rearrangement only by cytogenetics or FISH.

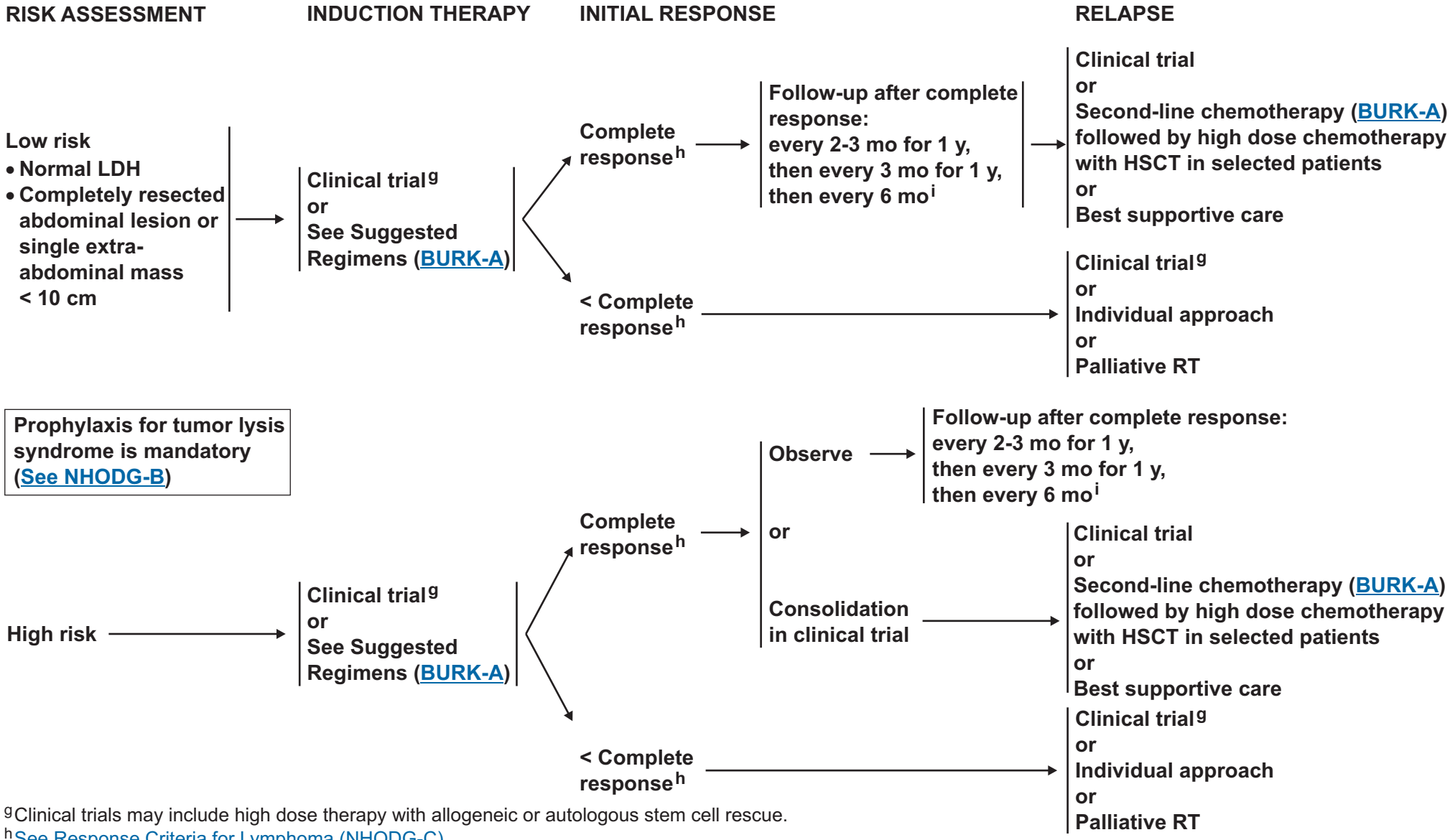
[d] See Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms (NHODG-A).

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

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[g] Clinical trials may include high dose therapy with allogeneic or autologous stem cell rescue.
[h] See Response Criteria for Lymphoma (NHODG-C).
[i] Relapse after 2 y is rare, therefore, follow-up should be individualized according to patient characteristics.

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SUGGESTED TREATMENT REGIMENS[a]
(in alphabetical order)

CHOP is not adequate therapy.

Induction therapy

Low Risk- Combination Regimens

- **CALGB 9251 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]).**
- **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 is 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 9251 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)**
- **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 is 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)

- **Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab (minimum 3 cycles with one additional cycle beyond CR) (regimen includes intrathecal methotrexate) (Data is for patients without CNS disease.)**
- **RIVAC (rituximab, ifosfamide, cytarabine, etoposide and intrathecal methotrexate) if have not received previously**
- **RGDP (rituximab, gemcitabine, dexamethasone, cisplatin)**
- **HDAC (high-dose cytarabine)**

See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)

[a] See references for regimens BURK-A 2 of 2.

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SUGGESTED TREATMENT REGIMENS
References

Low Risk- Combination Regimens

CALGB 9251 regimen

Lee EJ, Petroni GR, Schiffer CA, et al. Brief-duration high-intensity chemotherapy for patients with small noncleaved-cell lymphoma or FAB L3 Acute Lymphocytic Leukemia: Results of Cancer and Leukemia Group B Study 9251. J Clin Oncol 2001;19:4014-4022.

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.

CODOX-M (original or modified) (cyclophosphamide, doxorubicin, vincristine with intrathecal methotrexate and cytarabine followed by high-dose systemic 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.

Dose-adjusted EPOCH plus rituximab (regimen includes IT methotrexate)

Dunleavy K, Little, RF, Pittaluga S, et al. A prospective study of Dose-Adjusted (DA) EPOCH with rituximab in adult patients with newly diagnosed Burkitt lymphoma: A regimen with high efficacy and low toxicity. 10th International Conference on Malignant Lymphomas Abstracts. Annals of Oncology. 2008;19(suppl_4): iv83-iv84 (Abstract 009)

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.

High Risk- Combination Regimens

CALGB 9251 regimen

Lee EJ, Petroni GR, Schiffer CA, et al. Brief-duration high-intensity chemotherapy for patients with small noncleaved-cell lymphoma or FAB L3 Acute Lymphocytic Leukemia: Results of Cancer and Leukemia Group B Study 9251. J Clin Oncol 2001;19:4014-4022.

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Dunleavy K, Little, RF, Pittaluga S, et al. A prospective study of Dose-Adjusted (DA) EPOCH with Rituximab in adult patients with newly diagnosed Burkitt lymphoma: A regimen with high efficacy and low toxicity. 10th International Conference on Malignant Lymphomas Abstracts. Annals of Oncology 2008;19(suppl_4): iv83-iv84 (Abstract 009).

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

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.

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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.
- Adequate immunophenotyping to establish diagnosis[b,c]
  - Paraffin panel: CD45 (LCA), CD20, CD79a, CD3, CD2, CD5, 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

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Additional immunohistochemical studies to establish lymphoma subtype
  - Frozen: kappa/lambda
  - Paraffin panel: CD22, CD4, CD8, cyclin D1
- Molecular genetic analysis to detect: antigen receptor gene rearrangements
- Cytogenetics or FISH: MYC; t(9;22); t(8;14) and variants

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 anthracenediones- 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 Clinical Assessment and Induction Therapy (BLAST-2)

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

[b] Typical immunophenotype: LBL-B: sIg-, CD10+/-, CD19+, CD20-/+, TdT+. LBL-T: sIg-, CD10-, CD19/20-, CD3-/+, CD4/8+/+, CD1a+/-, TdT+, CD2+, CD7+.

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

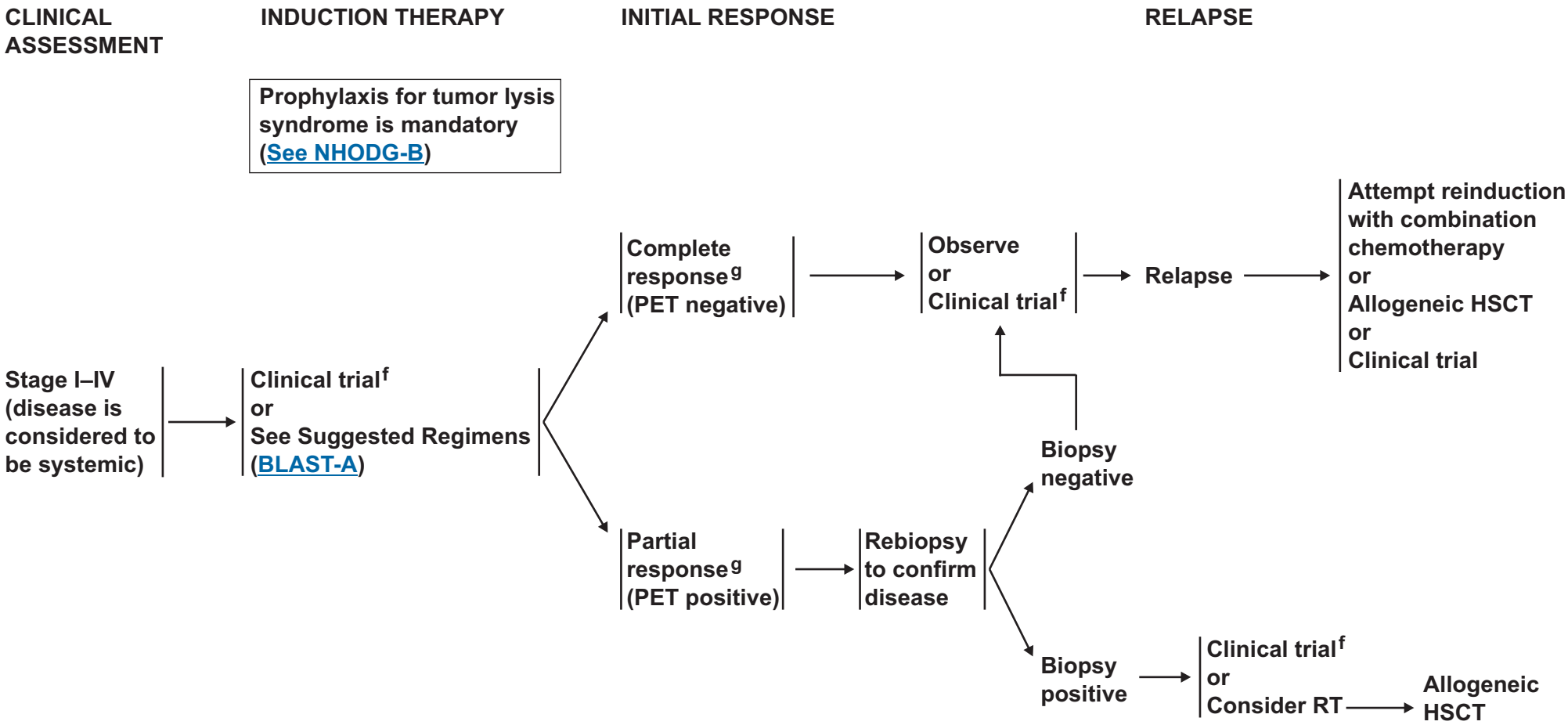
[d] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check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

[e] 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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[f]For poor risk patients, consideration of high dose therapy with autologous or allogeneic stem cell rescue is appropriate.
[g]See Response Criteria for Lymphoma (NHODG-C).

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SUGGESTED TREATMENT REGIMENS[a]
(in alphabetical order)

BFM (Berlin–Frankfurt–Munster)

- **Standard BFM regimen:**
  - **Induction phase:**
    - **Vincristine, daunomycin, prednisone, L-asparaginase, cytarabine (IT), and methotrexate (IT).**
  - **Consolidation phase (5 weeks):**
    - **Prednisone, cyclophosphamide, mercaptopurine, vincristine, cytarabine, IT methotrexate, and RT.**
  - **Interim Maintenance phase (8 weeks):**
    - **Mercaptopurine and methotrexate (PO)**
  - **Delayed intensification (7 weeks):**
    - ***Reinduction phase (4 weeks):***
      - **Dexamethasone, vincristine, and doxorubicin.**
    - ***Reconsolidation phase (3 weeks)*:**
      - **L-asparaginase, vincristine, cyclophosphamide, thioguanine, cytarabine, and intrathecal methotrexate.**
  - **Long-term maintenance (12 weeks):**
    - **Vincristine, prednisone, mercaptopurine, methotrexate (PO and IT).**

- **Augmented BFM regimen:**
  - **Induction I:**
    - **Prednisone, vincristine, daunorubicin, L-asparaginase, methotrexate (IT).**
  - **Induction II:**
    - **Cyclophosphamide, cytarabine, 6-mercaptopurine, methotrexate (IT)**
  - **Consolidation I:**
    - **Cytarabine, mitoxantrone, methotrexate, asparaginase, 6-mercaptopurine**
  - **Reinduction I**
    - **Prednisolone, vincristine, doxorubicin**
    - **Triple prophylaxis: methotrexate, cytarabine, dexamethasone**
  - **Reinduction II**
    - **Cyclophosphamide, cytarabine, 6-thioguanine**
    - **Triple prophylaxis: methotrexate, cytarabine, dexamethasone**
  - **Consolidation II**
    - **Etoposide, cytarabine**
    - **Cyclophosphamide, cytarabine**

Suggested Treatment Regimens continued on BLAST-A 2 of 3

[a] See references for regimens BLAST-A 3 of 3.

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SUGGESTED TREATMENT REGIMENS[a]
(in alphabetical order)

- **CALGB ALL regimen**
  - Induction therapy (4 weeks):
    - Cyclophosphamide, daunorubicin, vincristine, prednisone, and L-asparaginase.
    - For patients 60 years and older: the doses of cyclophsphamide, daunorubicin, and prednisone are modified (see reference for details).
  - Early intensification (4 weeks):
    - Intrathecal methotrexate, cyclophosphamide, 6-mercaptopurine, cytarabine, vincristine, and L-asparaginase.
  - CNS prophylaxis and interim maintenance:
    - Cranial irradiation in select cases, intrathecal methotrexate, 6-mercaptopurine, and methotrexate (PO).
  - Late intensification (8 weeks):
    - Doxorubicin, vincristine, dexamethasone, cyclophosphamide, 6-thioguanine, and cytarabine.
  - Prolonged maintenance (until 24 months from diagnosis):
    - Vincristine, prednisone, methotrexate (PO), and 6-mercaptopurine.

- **HyperCVAD[b] (cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with methotrexate + cytarabine, including intrathecal methotrexate**
  - Maintenance therapy
    - 6-mercaptopurine, methotrexate, vincristine, and prednisone (POMP)
  - In the cases of CD20 positive (≥ 20%) acute lymphoblastic lymphoma (ALL), the addition of rituximab should be considered.
  - In cases of Philadelphia chromosome positive ALL, imatinib should be incorporated into regimen.

- **LMB-86 regimen**
  - Cytoreductive therapy
    - COP (cyclophosphamide, vincristine, and prednisone)
  - Induction therapy
    - COPADM (cyclophosphamide, vincristine, prednisone, doxorubicin, and high-dose methotrexate)
  - Consolidation therapy
    - CYVE (cytarabine and etoposide; regimen includes high-dose cytarabine)

- **Maintenance chemotherapy**
  - Up to 2 y of maintenance based on the treatment protocol is recommended.

See Suggested Treatment Regimens on BLAST-A 1 of 3

[a] See references for regimens BLAST-A 3 of 3.

[b] For T-cell lymphoblastic lymphomas with primary mediastinal presentation, residual masses are irradiated.

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SUGGESTED TREATMENT REGIMENS
References

BFM (Berlin–Frankfurt–Munster)
Standard BFM
Stock W, La M, Sanford B, et al. What determines the outcomes for adolescents and young adults with acute lymphoblastic leukemia treated on cooperative group protocols? A comparison of Children's Cancer Group and Cancer and Leukemia Group B studies. Blood 2008;112:1646-1654.
Augmented BFM
Hoelzer D, Gokbuget N, Digel W, et al. Outcome of adult patients with T-lymphoblastic lymphoma treated according to protocols for acute lymphoblastic leukemia. Blood 2002;99:4379-4385.

CALGB ALL regimen
Larson R, Dodge R, Burns C, et al. A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: cancer and leukemia group B study 8811. Blood 1995;85:2025-2037.

HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate-cytarabine) followed by POMP (mercaptopurine, methotrexate, vincristine, and prednisone) maintenance
Kantarjian HM, O'Brien S, Smith TL, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. J Clin Oncol 2000;18:547-561.
Thomas DA, O'Brien S, Cortes J, et al. Outcome with the hyper-CVAD regimens in lymphoblastic lymphoma. Blood 2004;104:1624-1630.

LMB-86 regimen
Soussain C, Patte C, Ostronoff M, et al. Small noncleaved cell lymphoma and leukemia in adults. A retrospective study of 65 adults treated with the LMB pediatric protocols. Blood 1995;85:664-674.

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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]
  - Recommended panel for paraffin section immunohistochemistry: 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, TdT, CD14, CD20
- Epstein-Barr virus (EBER-ISH)

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Additional immunohistochemical studies to establish lymphoma subtype
  - DLBCL, Burkitt, Plasmablastic, Primary effusion: CD10, BCL2, Ki-67, BCL6, CD138
- Molecular genetic 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
- Viral load
- Hepatitis B testing[b]
- MUGA scan/echocardiogram if anthracycline or anthracenediones- 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

→ See Treatment and Follow-up (AIDS-2) and (AIDS-3)

[a] See Use of Immunophenotyping and Genetic Tesitng in Differential Diagnosis of Mature B-cell and T/NK-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.

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

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:[d]**
  - **CODOX-M/IVAC: cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate alternating with ifosfamide, etoposide, high-dose cytarabine ± rituximab[e]**
  - **Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) ± rituximab[e] (+ rituximab is for favorable presentation)**
  - **CDE (cyclophosphamide, doxorubicin, etoposide) ± rituximab[e] (+ rituximab is for favorable presentation)**
  - **Consider CHOP with high-dose methotrexate ± rituximab[e] (+ rituximab is for favorable presentation) Avoid methotrexate dose > 3 g/m^2**
- **GCSF for all patients**

- **Lymphoma associated with Castleman's disease**
- **Diffuse large B-cell lymphoma**
- **Primary effusion lymphoma[c]**

→

- **Suggested regimens:[d]**
  - **Dose-adjusted EPOCH**
  - **CDE**
  - **CHOP**
  - **CDOP (cyclophosphamide, liposomal doxorubicin, vincristine, prednisone)**
- **GCSF for all patients**
- **Intrathecal therapy (IT)[f]**
- **If CD20+, add rituximab with chemotherapy[e]**

→ **For DLBCL relapse, see BCEL-6**

See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)

[c] Most cases are CD20 negative and addition of rituximab is not indicated.

[d] See references for regimens AIDS-A.

[e] Patients on active antiretrovirals with persistently low CD4 count of <100 tend to have poor prognosis and higher risk of infection associated with the addition of 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. 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.

[f] Prophylactic IT methotrexate is used at some NCCN institutions for all patients. At other NCCN institutions, patients with HIV-associated DLBCL receive IT methotrexate in selective settings (paranasal sinus, testicular, epidural, bone marrow with large cell lymphoma, HIV-lymphoma, or ≥ 2 extranodal sites).

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TREATMENT AND FOLLOW-UP

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[g] →

- **Suggested regimens:[d]**
  - **CODOX-M/IVAC**
  - **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 CNS Guidelines- Primary CNS Lymphoma**
- **Best Supportive Care (See NCCN Palliative Care Guidelines)**

See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)

[d] See references for regimens AIDS-A.
[g] Management can also apply to HIV negative plasmablastic lymphoma.

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SUGGESTED TREATMENT REGIMENS
References

CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate alternating with ifosfamide, etoposide, high-dose cytarabine)
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

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.

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). ASH Annual Meeting Abstracts. 2008;112:1467.

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
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.

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NCCN Guidelines™ Version 1.2011
Primary Cutaneous B-Cell Lymphoma[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]
  - Recommended panel for paraffin section immunohistochemistry: CD20, CD79a, CD3, CD5, CD10, BCL2, BCL6, Ki-67, kappa/lambda, IRF4/MUM1

USEFUL IN CERTAIN CIRCUMSTANCES:

- Additional immunohistochemical studies to establish lymphoma subtype
  - Paraffin panel: cyclin D1
  - Assessment of surface IgM and IgD expression (to further help in distinguishing DLBCL, leg type from follicle center lymphoma)
- Molecular genetic analysis to detect: antigen receptor gene rearrangements; IgH gene rearrangement by PCR
- Cytogenetics or FISH: t(14;18)

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.

WORKUP

ESSENTIAL:[d]

- Complete history and physical examination-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

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

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

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

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

[a] For non-cutaneous, see Nongastric MALT Lymphoma (NGMLT-1).

[b] See Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-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.

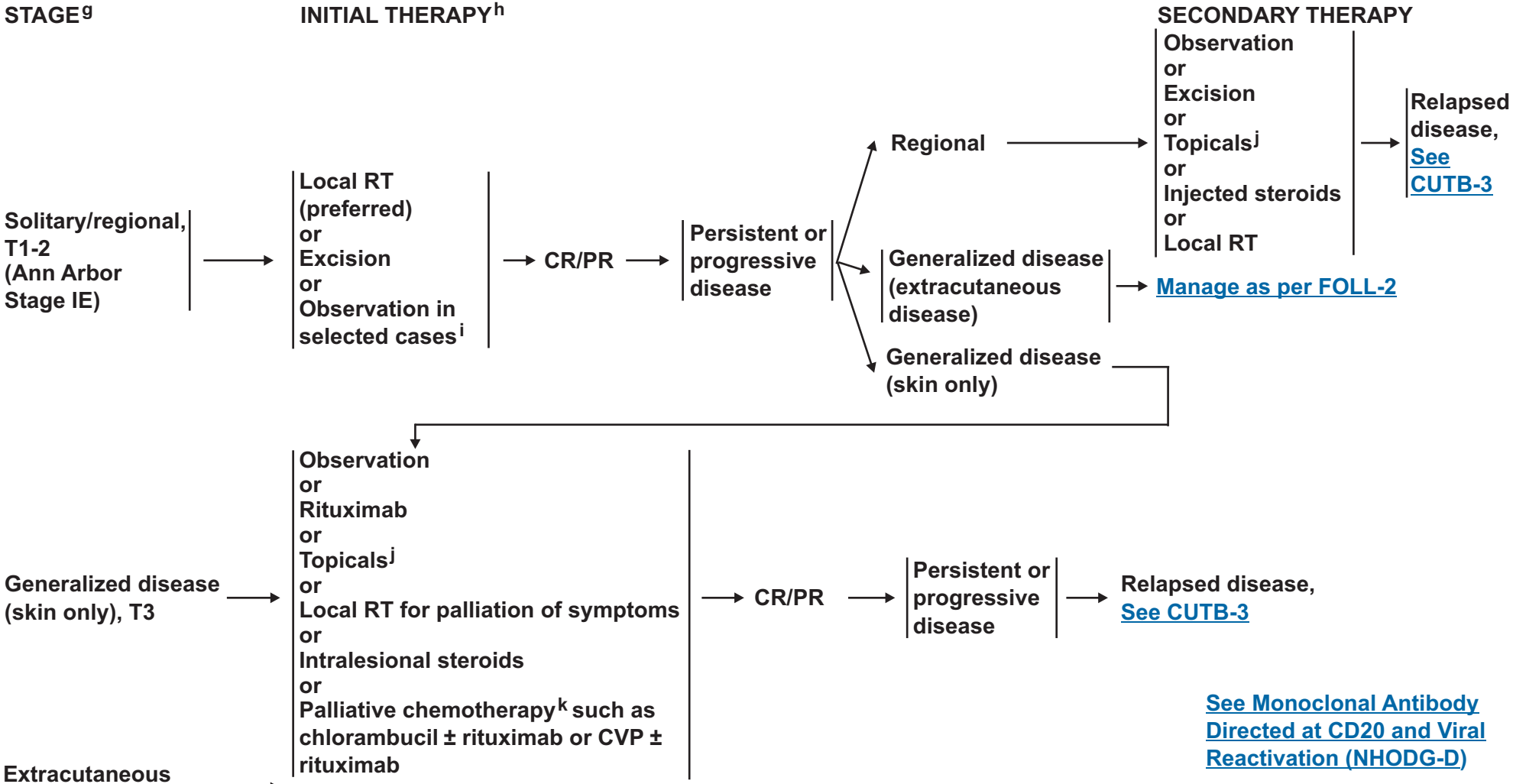
[e] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check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

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PRIMARY CUTANEOUS MARGINAL ZONE OR FOLLICLE CENTER B-CELL LYMPHOMA[f]



See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)

[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 not feasible nor desired.

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

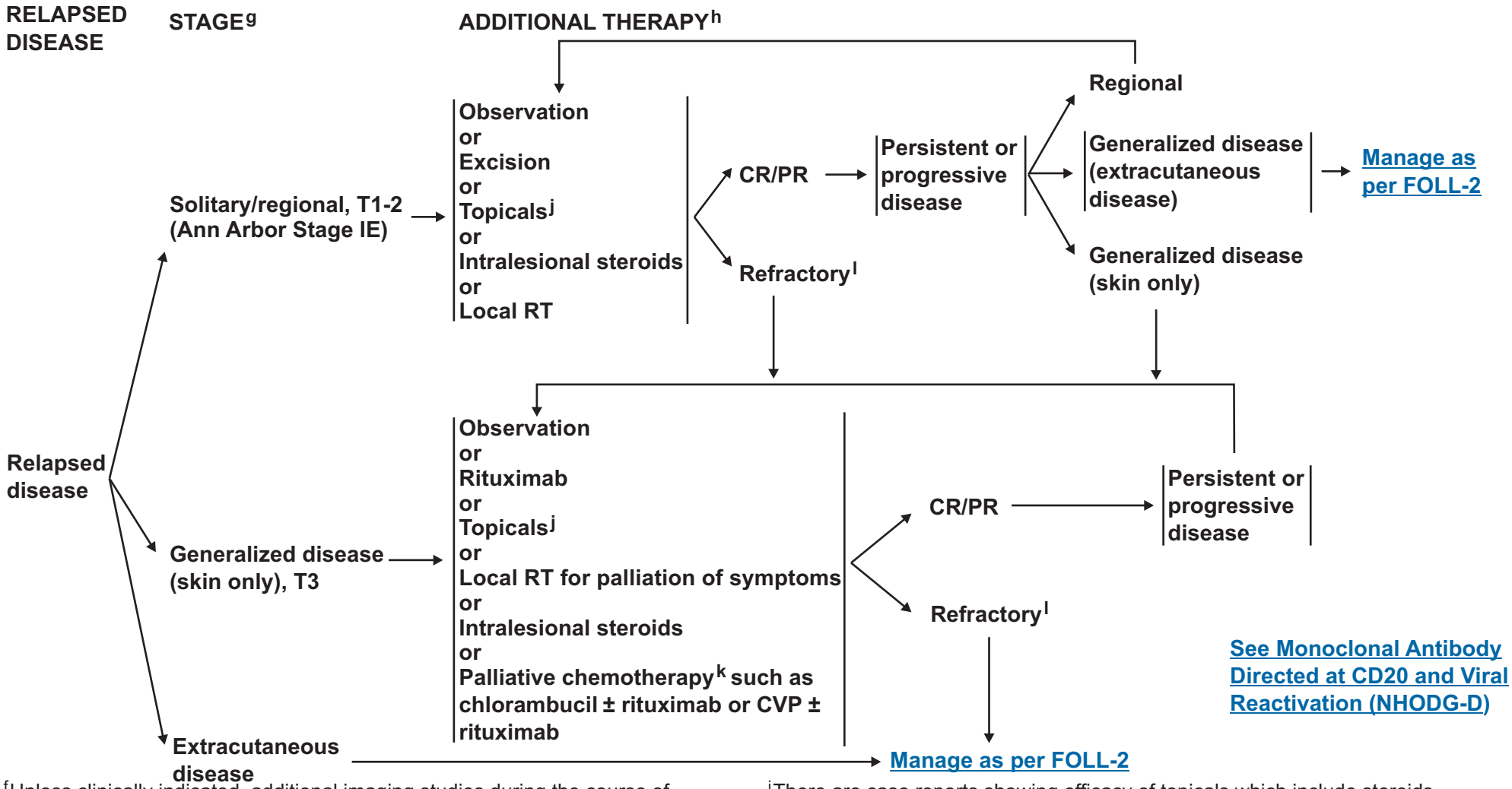
[k] In rare circumstances for very extensive disease, other combination chemotherapy regimens listed in FOLL-B are used.

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PRIMARY CUTANEOUS MARGINAL ZONE OR FOLLICLE CENTER B-CELL LYMPHOMA[f]



[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, bexarotene.

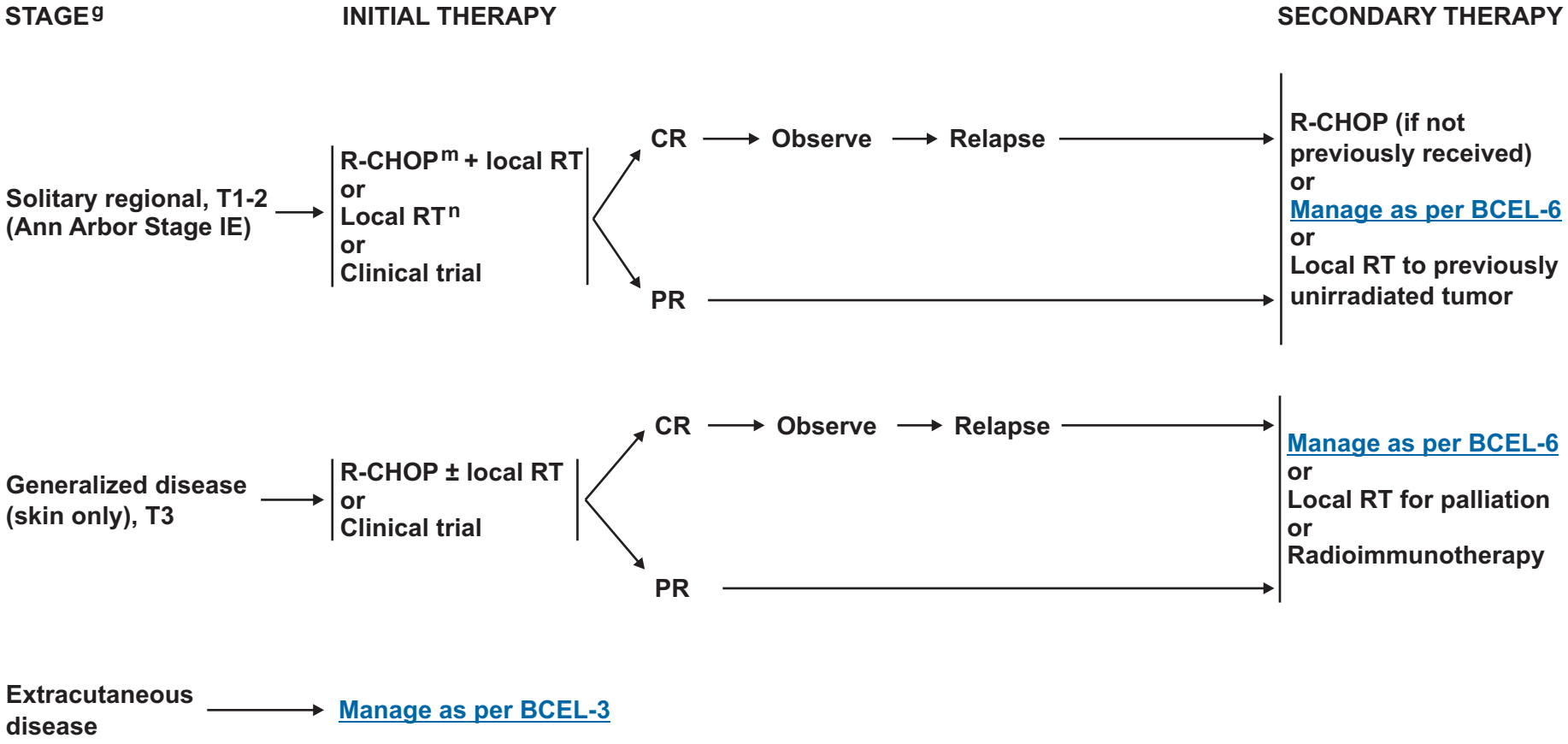
[k] In rare circumstances for very extensive disease, other combination chemotherapy regimens listed in FOLL-B are used.

[l] Refractory to all previous treatments.

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PRIMARY CUTANEOUS DIFFUSE LARGE B-CELL LYMPHOMA, LEG TYPE



See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)

[g] See TNM Classification of Cutaneous Lymphoma other than MF/SS (CUTB-A).
[m] For alternate regimens, see BCEL-C.
[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).

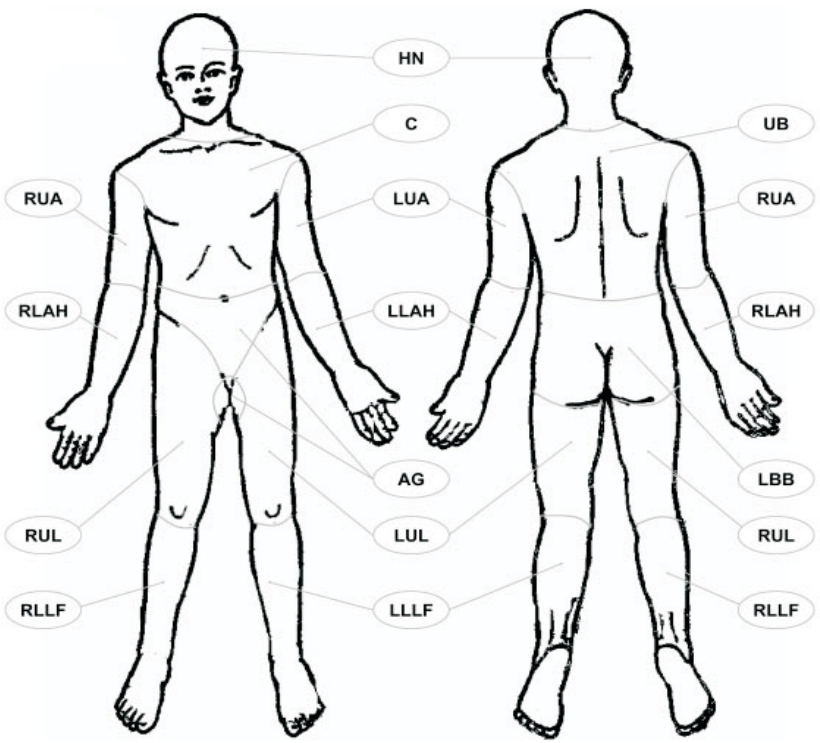
[c] Definition of lymph node regions is consistent with the Ann Arbor system: Peripheral sites: antecubital, cervical, supraclavicular, axillary, inguinal-femoral, and popliteal. Central sites: mediastinal, pulmonary hilar, paraortic, iliac.

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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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Rituximab

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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.

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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.

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

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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 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]**
  - **Recommended panel for paraffin section immunohistochemistry: CD20, CD3, CD10, BCL6, Ki-67, CD5, CD30, CD2, CD4, CD8, CD7, CD56, CD57 CD21, CD23, EBER, ALK**
    or
  - **Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD3, CD5, CD19, CD10, CD20, CD30, CD4, CD8, CD7, CD2**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **Molecular genetic analysis to detect: antigen receptor gene rearrangements; t(2;5) and variants**
- **Additional immunohistochemical studies to establish lymphoma subtype: βF1, CD279**
- **Cytogenetics or FISH**
- **CXCL-13, PD-1**

SUBTYPES

Subtypes included:

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

→ **See Workup (TCEL-2)**

Subtypes *not* included:

- **Primary cutaneous ALCL**
- **All other T-cell lymphomas**

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

[a] Molecular diagnosis for T-cell receptor rearrangements should be done in most circumstances to confirm clonality. T-cell receptors rearrangements alone are not sufficient for diagnosis.

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

[c] AITL may occasionally present with concurrent DLBCL. EBV and appropriate immunohistochemistry should be performed.

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WORKUP

ESSENTIAL:[d]
- Physical exam: attention to node-bearing areas, including Waldeyer's ring, size of liver and spleen, skin rash and 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
- Calculation of International Prognostic Index (IPI)[e]
- MUGA scan/echocardiogram if anthracycline or anthracenediones- based regimen is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

USEFUL IN SELECTED CASES:
- PET-CT scan
- Neck CT
- Head CT or MRI
- Skin biopsy
- Discussion of fertility issues and sperm banking
- HIV, HTLV-1

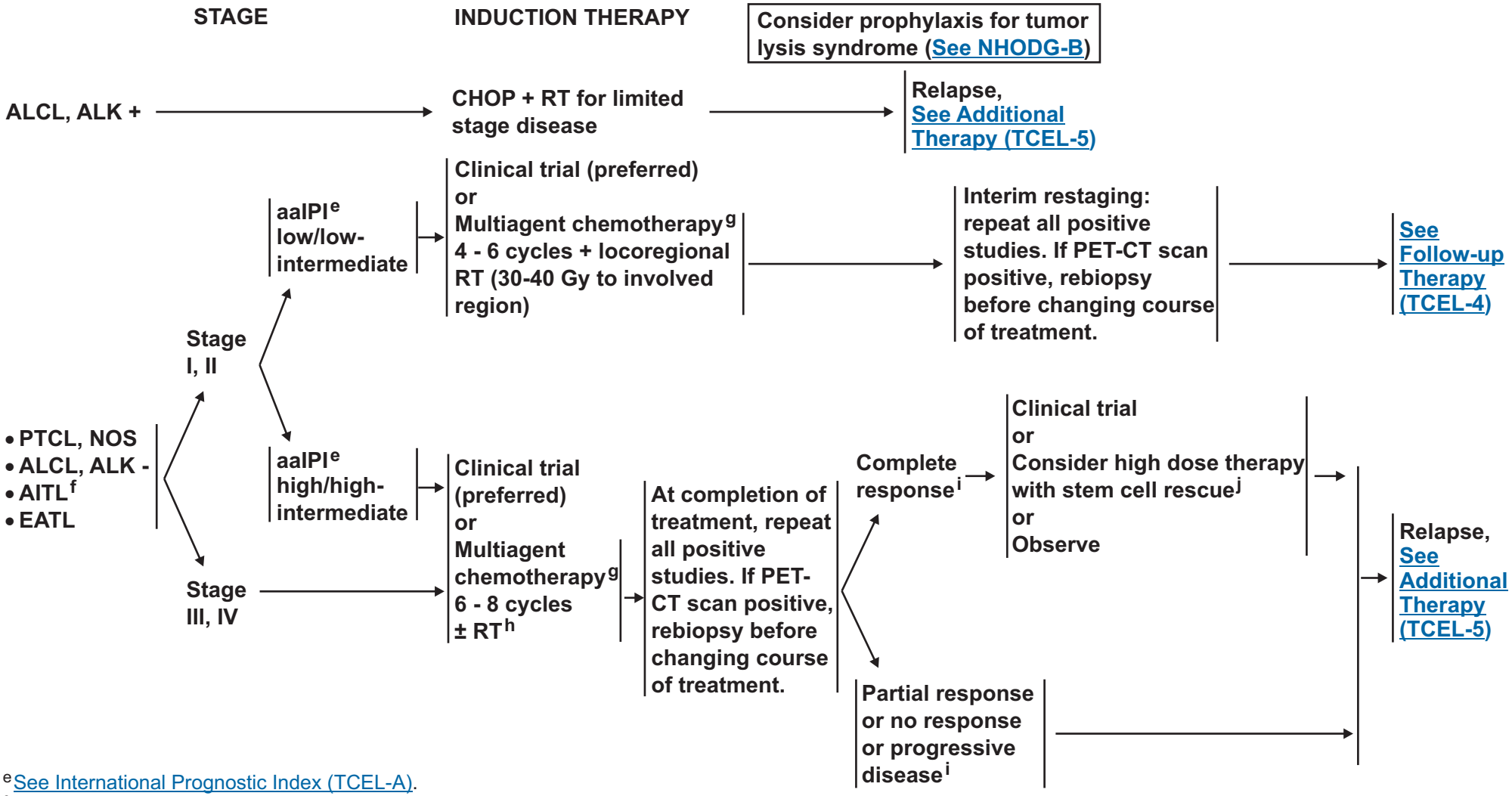
→ See Induction Therapy (TCEL-3)

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

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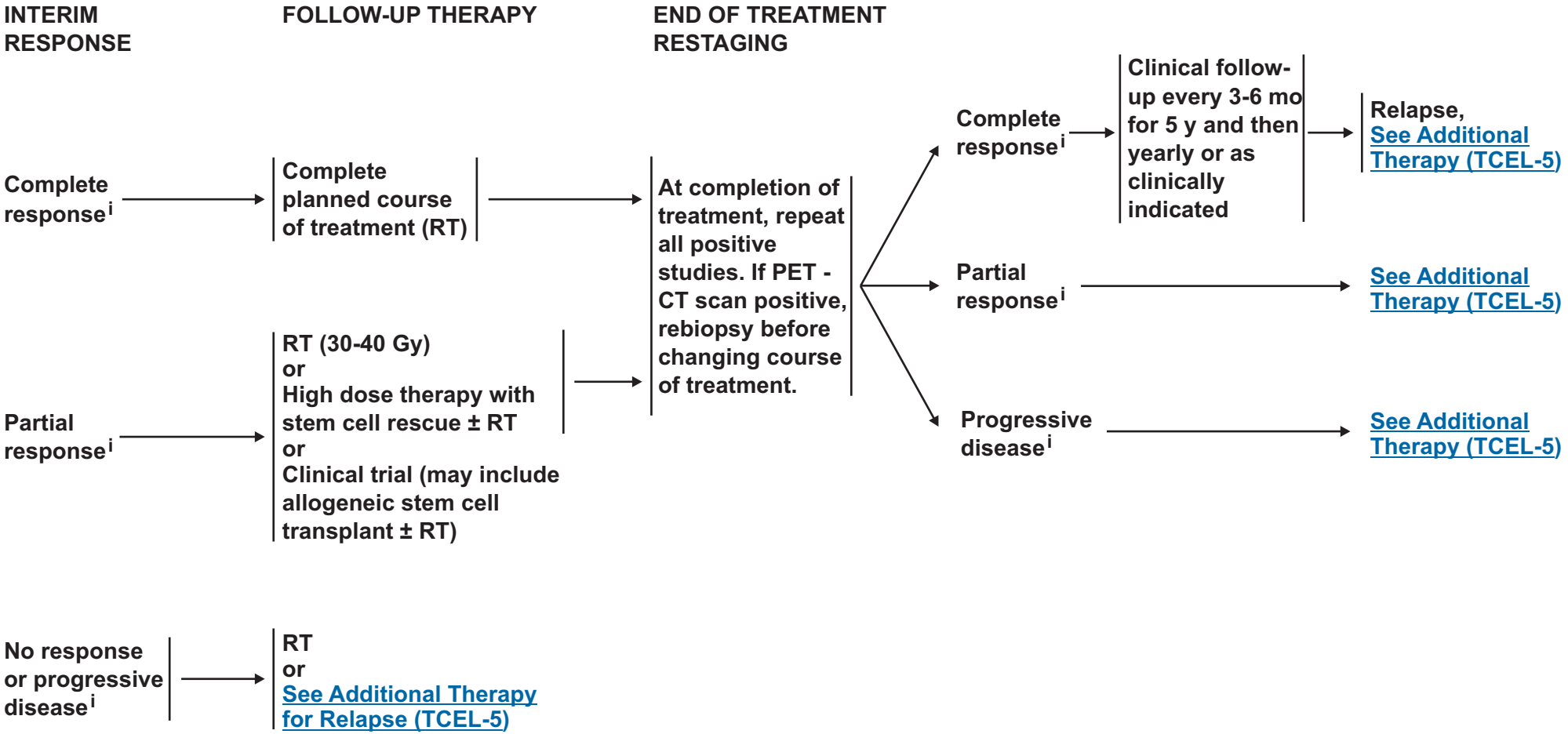
[e] See International Prognostic Index (TCEL-A).
[f] For selected patients (elderly, comorbid conditions), a trial of single agent corticosteroid may be considered for symptom management.
[g] See Suggested Treatment Regimens (TCEL-B).
[h] Patients with locoregional disease receive RT.
[i] See Response Criteria for Lymphoma (NHODG-C).
[j] Localized areas can be irradiated before or after high dose therapy.

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STAGE I/II, LOW/LOW- INTERMEDIATE

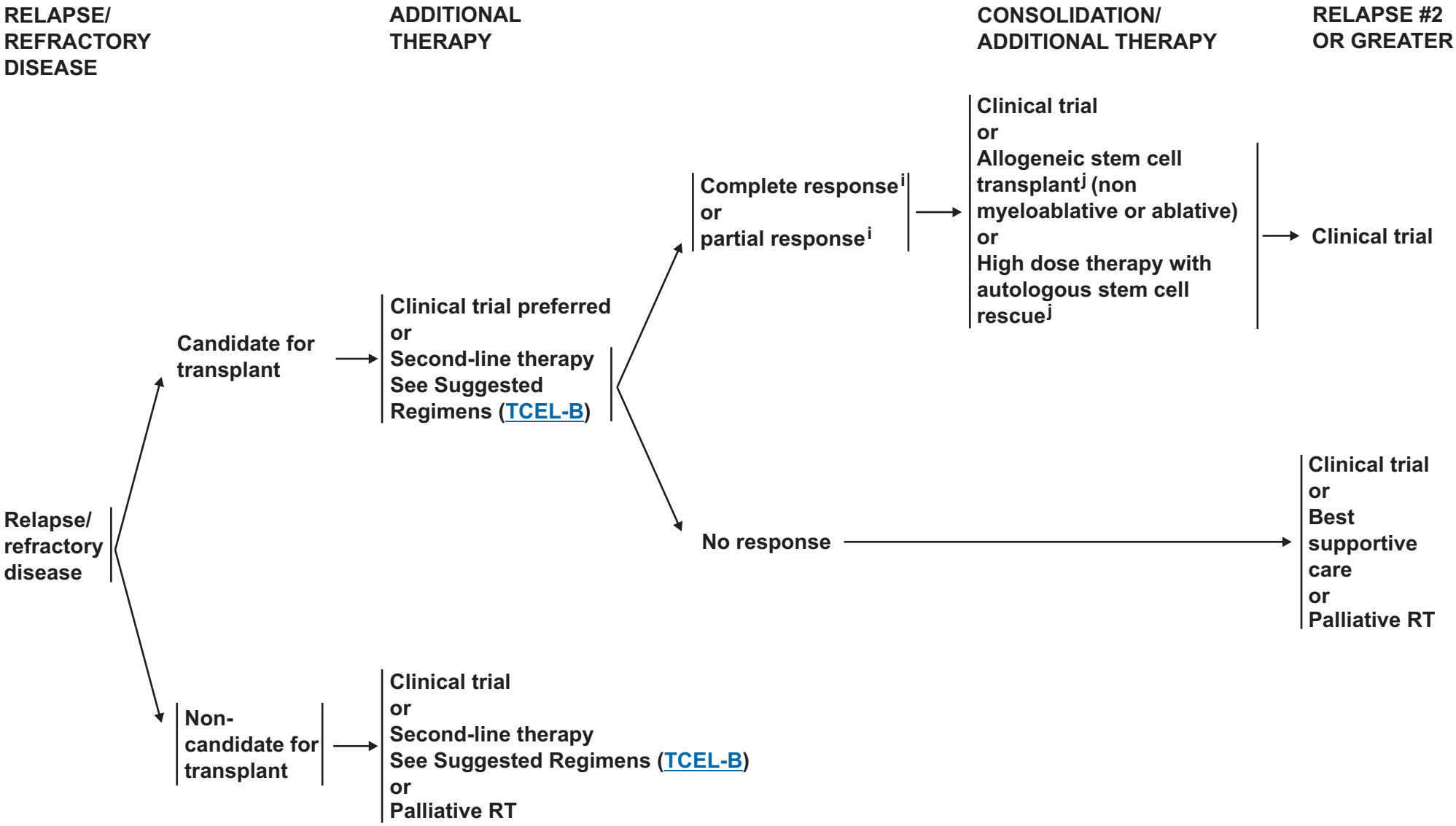


[i] See Response Criteria for Lymphoma (NHODG-C).

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[i] See Response Criteria for Lymphoma (NHODG-C).

[j] Localized areas can be irradiated before or after high dose therapy.

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INTERNATIONAL PROGNOSTIC INDEX[a]

ALL PATIENTS:	INTERNATIONAL INDEX, ALL PATIENTS:	
• Age > 60 years	• Low	0 or 1
• Serum LDH > 1 x normal	• Low intermediate	2
• Performance status 2-4	• High intermediate	3
• Stage III or IV	• High	4 or 5
• Extranodal involvement > 1 site		

AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX[a]

PATIENTS ≤ 60 YEARS:	INTERNATIONAL INDEX, PATIENTS ≤ 60 YEARS:	
• Stage III or IV	• Low	0
• Serum LDH > 1 x normal	• Low/intermediate	1
• Performance status 2-4	• High/intermediate	2
	• High	3

Prognostic Index for PTCL-U (PIT)[b]

RISK FACTORS:	PROGNOSTIC RISK:	
• Age > 60 years	• Group 1	0
• Serum LDH > 1 x normal	• Group 2	1
• Performance status 2-4	• Group 3	2
• Bone marrow involvement	• Group 4	3 or 4

[a] Adapted with permission, The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-hodgkin's lymphoma. N Engl J Med 329:987-994, 1993. Copyright © 1993 Massachusetts Medical Society. All rights reserved.

[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:[b]
- Clinical trial preferred
- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) appropriate for ALCL, ALK+.
- Other regimens that can be used include:
  - CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone)
  - CHOP every 2 or 3 wks
  - CHOP followed by ICE (ifosfamide, carboplatin, etoposide)
  - CHOP followed by IVE (ifosfamide, etoposide and epirubicin) alternating with intermediate dose methotrexate [New Castle Regimen]
  - HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine

First-line Consolidation:
- All patients, except low risk (aaIPI), consider consolidation with high dose therapy and stem cell rescue. (ALCL, ALK positive is a subtype with good prognosis and does not need consolidative transplant if in remission.)

Second-line therapy (candidate for transplant):
- Clinical trial preferred
- DHAP (dexamethasone, cisplatin, cytarabine)
- ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)
- GDP (gemcitabine, dexamethasone, cisplatin)
- GemOx (gemcitabine, oxaliplatin)
- ICE (ifosfamide, carboplatin, etoposide)
- MINE (mesna, ifosfamide, mitoxantrone, etoposide)
- Pralatrexate (category 2B)[c]

Second-line therapy (non-candidate for transplant):
- Clinical trial preferred
- Alemtuzumab[d]
- Bortezomib[d]
- Cyclosporine for AITL only[e]
- Denileukin diftitox
- Gemcitabine
- Pralatrexate[c]
- Radiation therapy

[a] See references for regimens TCEL-B 2 of 2.
[b] Standard induction for PTCL remains undefined with the exception of ALCL, ALK + for which CHOP remains the standard. Clinical trial is preferred for all other subtypes.
[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(3):634-41.

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. ASH Annual Meeting Abstracts. 2005;106:2679.

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. ASH Annual Meeting Abstracts. 2009;114:1660.

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 et al. Prognosis and treatment of patients with peripheral T-cell lymphoma: The M. D. Anderson Cancer Center experience. 2010 ASCO Annual Meeting Abstract 8051.

Second-line therapy (candidate for transplant)

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.

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.

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.

Second-line therapy (non-candidate for transplant)

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.

Cyclosporine for AILT

Advani R, Horwitz S, Zelenetz A, Horning SJ. Angioimmunoblastic T cell lymphoma: treatment experience with cyclosporine. Leuk Lymphoma 2007;48:521-525.

Denileukin diftitox

Talpur R, Apisarnthanarax N, Ward S, Duvic M. Treatment of refractory peripheral T-cell lymphoma with denileukin diftitox (ONTAK). Leuk Lymphoma 2002;43:121-126.

Dang NH, Pro B, Hagemeister FB, et al. Phase II trial of denileukin diftitox for relapsed/refractory T-cell non-Hodgkin lymphoma. Br J Haematol 2007;136:439-447.

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.

Pralatrexate

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). ASCO Meeting Abstracts. 2009: 8561.

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National Comprehensive Cancer Network®

NCCN Guidelines™ Version 1.2011
Mycosis Fungoides/Sezary Syndrome

NCCN Guidelines Index
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Discussion

DIAGNOSIS

ESSENTIAL:

- Biopsy of suspicious skin sites
- Dermatopathology review of slides

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Immunohistochemical studies of skin biopsy[a,b] (CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, CD26, CD56, TIA1, granzyme B, βF1)
- Molecular study for T-cell receptor (TCR) gene rearrangements (assessment of clonality) of skin biopsy;[a] PCR methods[c]
- Assessment of peripheral blood for Sezary cells (in cases where skin is not diagnostic, especially T4) including Sezary cell prep, flow cytometry and PCR for TCR gene rearrangement
- Biopsy of suspicious lymph nodes (in absence of definitive skin diagnosis)
- Assessment of ATLL serology or PCR in at-risk populations

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:[d]
  - CBC with Sezary screen (manual slide review, "Sezary cell prep")
  - Sezary flow cytometric study (optional for T1); 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
  - TCR gene rearrangement of peripheral blood lymphocytes if Sezary Syndrome suspected
  - Comprehensive metabolic panel
  - LDH
- Imaging studies
  - Neck/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[e]

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 or 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

STAGE (MFSS-2)

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)

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

[c] 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 Mycosis Fungoides/Sezary Syndrome. Demonstration of identical clones in skin, blood and/or lymph node may be helpful in selected cases.

[d] Sezary syndrome (B2) is as defined on MFSS-2.

[e] Many skin-directed and systemic therapies are contraindicated or of unknown safety in pregnancy. Refer to individual drug information.

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TNMB[f]		TNMB Classification and Staging of Mycosis Fungoides and Sezary Syndrome[g]
Skin	T1	Limited patches,[h] papules and/or plaques[i] covering < 10 % of the skin surface
	T2	Patches,[h] papules and/or plaques[i] covering ≥ 10 % of the skin surface
	T3	One or more tumors[j] (≥ 1 cm in diameter)
	T4	Confluence of erythema ≥ 80 % body surface area
Node	N0	No clinically abnormal peripheral lymph nodes; biopsy not required[k]
	N1	Clinically abnormal peripheral lymph nodes; histopathology Dutch Gr 1 or NCI LN 0-2
	N2	Clinically abnormal peripheral lymph nodes; histopathology Dutch Gr 2 or NCI LN 3
	N3	Clinically abnormal peripheral lymph nodes; histopathology Dutch Gr 3-4 or NCI LN 4
	NX	Clinically abnormal peripheral lymph nodes; no histologic confirmation
Visceral	M0	No visceral organ involvement
	M1	Visceral involvement (must have pathology confirmation[l] and organ involved should be specified)
Blood	B0	Absence of significant blood involvement: ≤ 5 % of peripheral blood lymphocytes are atypical (Sezary) cells[m]
	B1	Low blood tumor burden: > 5 % of peripheral blood lymphocytes are atypical (Sezary) cells but does not meet the criteria of B2
	B2	High blood tumor burden: ≥ 1000/mcL Sezary cells[l]

[f] Olsen E, Vonderheid E, Pimpinelli N, et al. Blood 2007;110:1713-1722.

[g] 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 more or increase in CD4 cells with an abnormal phenotype (40% CD4/CD7 or 30% CD4/CD26).

[h] Patch = Any size skin lesion without significant elevation or induration. Presence/absence of hypo- or hyperpigmentation, scale, crusting and/or poikiloderma should be noted.

[i] Plaque = Any size skin lesion that is elevated or indurated. Presence or absence of scale, crusting and/or poikiloderma should be noted. Histological features such as folliculotropism or large cell transformation (≥ 25 % large cells), CD30+ or CD30- and clinical features such as ulceration are important to document.

[j] 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 histological evidence of large cell transformation has occurred. Phenotyping for CD30 is encouraged.

[k] Abnormal peripheral lymph node(s) = any palpable peripheral node that on physical examination is firm, irregular, clustered, fixed or ≥ 1.5 cm in diameter. Node groups examined on physical examination = cervical, supraclavicular, epitrochlear, axillary and inguinal. Central nodes, which are not generally amenable to pathologic assessment, are not currently considered in the nodal classification unless used to establish N3 histopathologically.

[l] Spleen and liver may be diagnosed by imaging criteria.

[m] Sezary cells are defined as lymphocytes with hyperconvoluted cerebriform nuclei. If Sezary cells are not able to be used to determine tumor burden for B2, then one of the following modified ISCL criteria along with a positive clonal rearrangement of the TCR may be used instead. (1) expanded CD4+ or CD3+ cells with CD4/CD8 ratio ≥ 10, (2) expanded CD4+ cells with abnormal immunophenotype including loss of CD7 or CD26.

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Clinical Staging/Classification of MF and SS[f]

	T	N	M	B
IA	1	0	0	0,1
IB	2	0	0	0,1
II	1-2	1,2	0	0,1
IIB	3	0-2	0	0,1
III	4	0-2	0	0,1
IIIA	4	0-2	0	0
IIIB	4	0-2	0	1
IVA_1	1-4	0-2	0	2
IVA_2	1-4	3	0	0-2
IVB	1-4	0-3	1	0-2

[f]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.

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STAGE (MFSS-2)

PRIMARY TREATMENT[o]

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)**

CR/PR[p] or inadequate response → **Relapse with or persistent T1 skin disease**

Refractory disease[q] 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**

Histologic evidence of folliculotropic or large cell transformed MF[n] → See Primary Treatment for Stage IIB on page MFSS-6

[n] Folliculotropic, large cell transformed MF, or B1 involvement has been associated with worse outcome, thus, may be managed as "tumor (IIB)" disease (MFSS-6) or stage III with B1 involvement (MFSS-7), respectively.

[o] It is preferred that treatment occur at centers with expertise in the management of the disease.

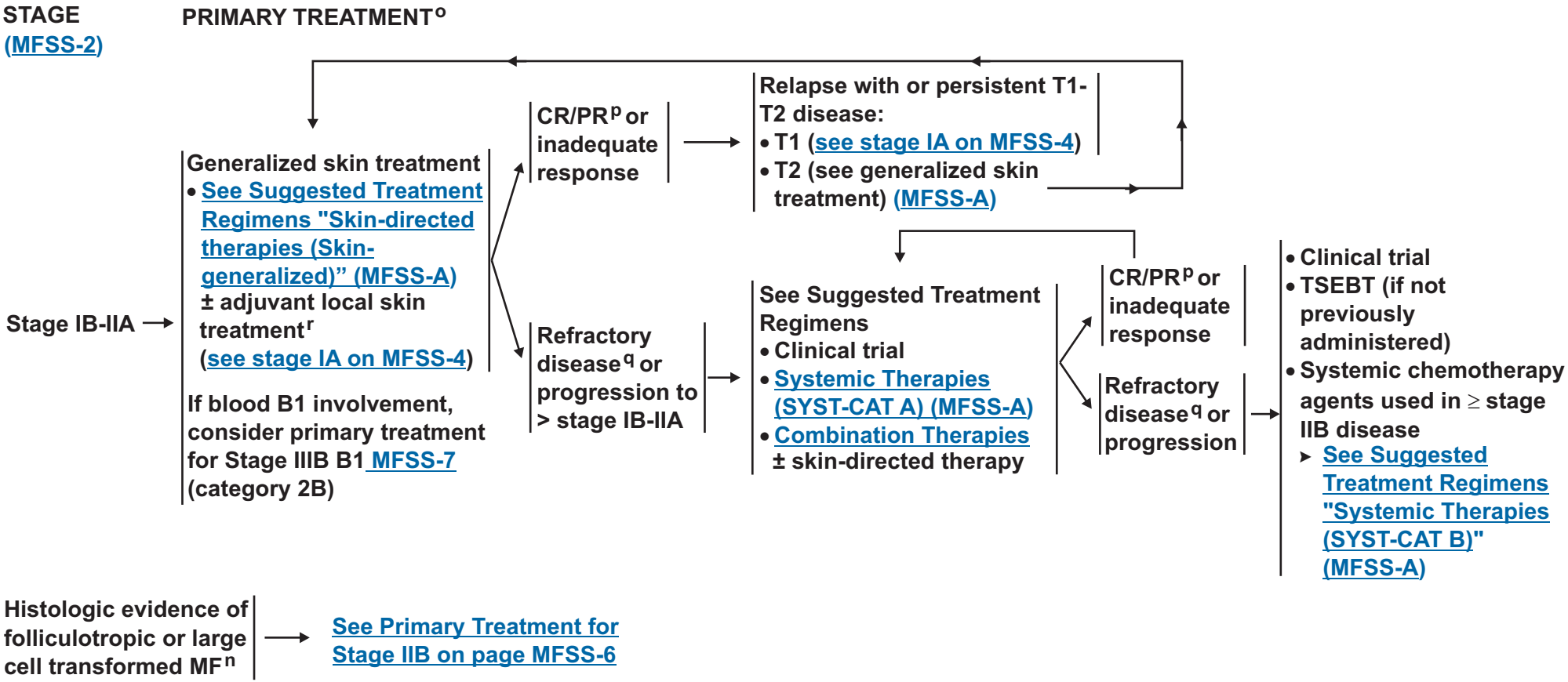
[p] Patients achieving a response should be considered for maintenance or taper regimens to optimize response duration. Patients who relapse often respond well to the same treatment. Patients with a PR should be treated with the other options in the primary treatment list to improve response before moving onto treatment for refractory disease. Patients with relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

[q] Refractory or intolerant to multiple previous therapies.

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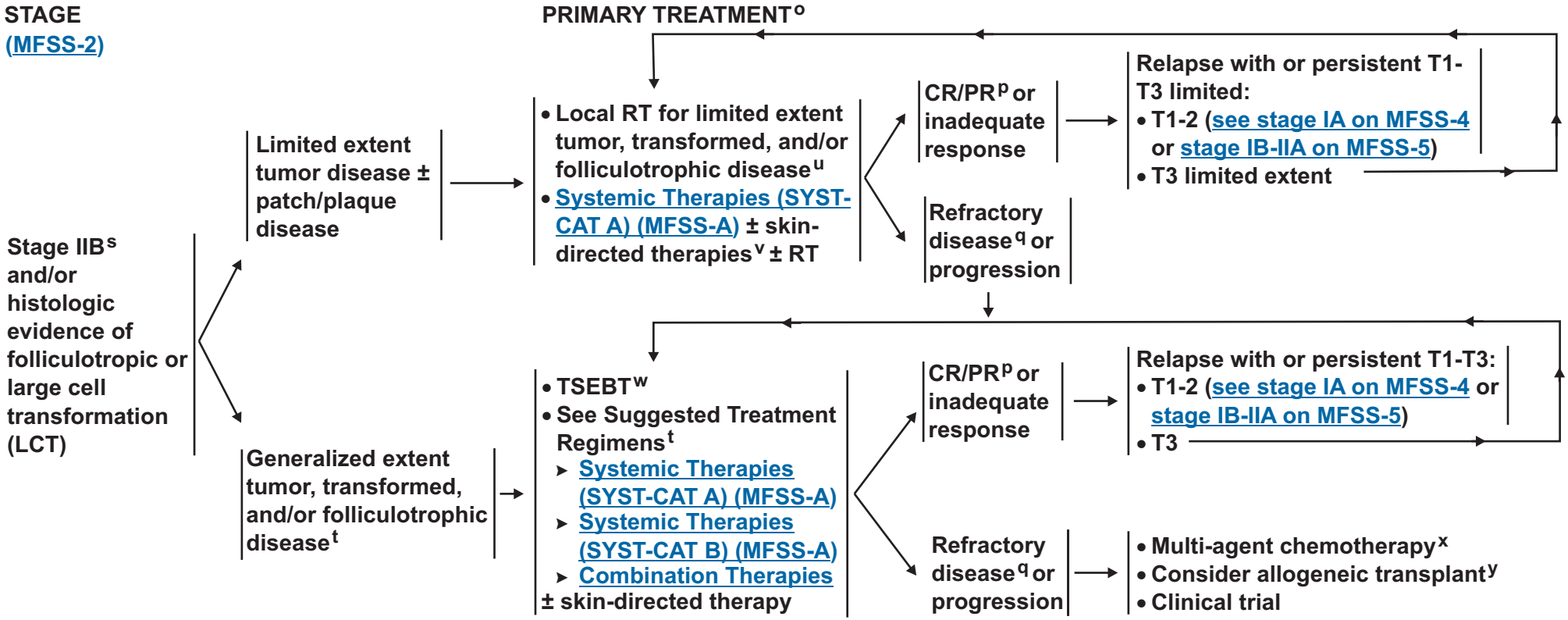
[q] Refractory or intolerant to multiple previous therapies.

[r] For patients with recalcitrant sites after generalized skin treatment, additional local treatment may be needed.

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[o] It is preferred that treatment occur at centers with expertise in the management of the disease.

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[q] Refractory or intolerant to multiple previous therapies.

[s] Rebiopsy if suspect large cell transformation.

[t] 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 category A or B are appropriate. If aggressive growth is seen, then agents listed in category C (SYST-CAT C) are preferred.

[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.

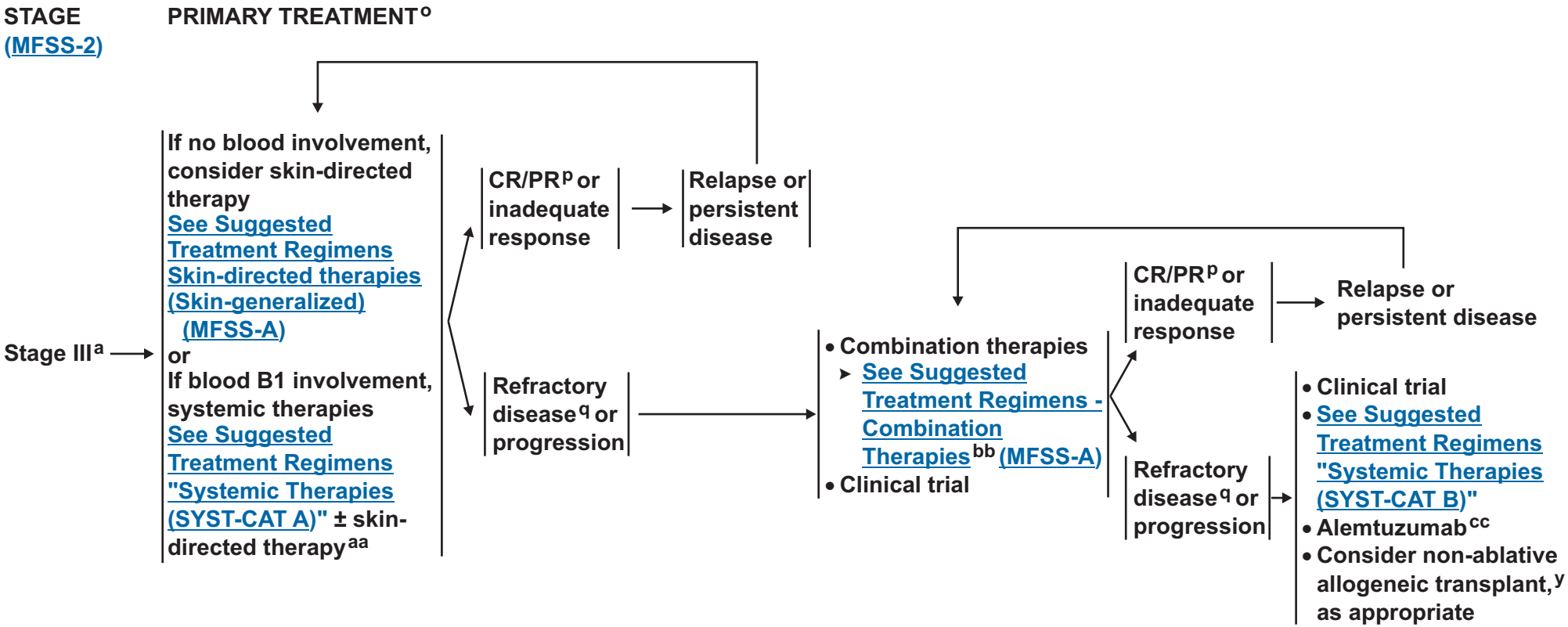
[x] Most patients are treated with multiple SYST-CAT A/B or Combination therapies before receiving multiagent chemotherapy.

[y] The role of allogeneic HSCT is controversial. See discussion for further details.

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[o] It is preferred that treatment occur at centers with expertise in the management of the disease.

[p] Patients achieving a response 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.

[q] 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.

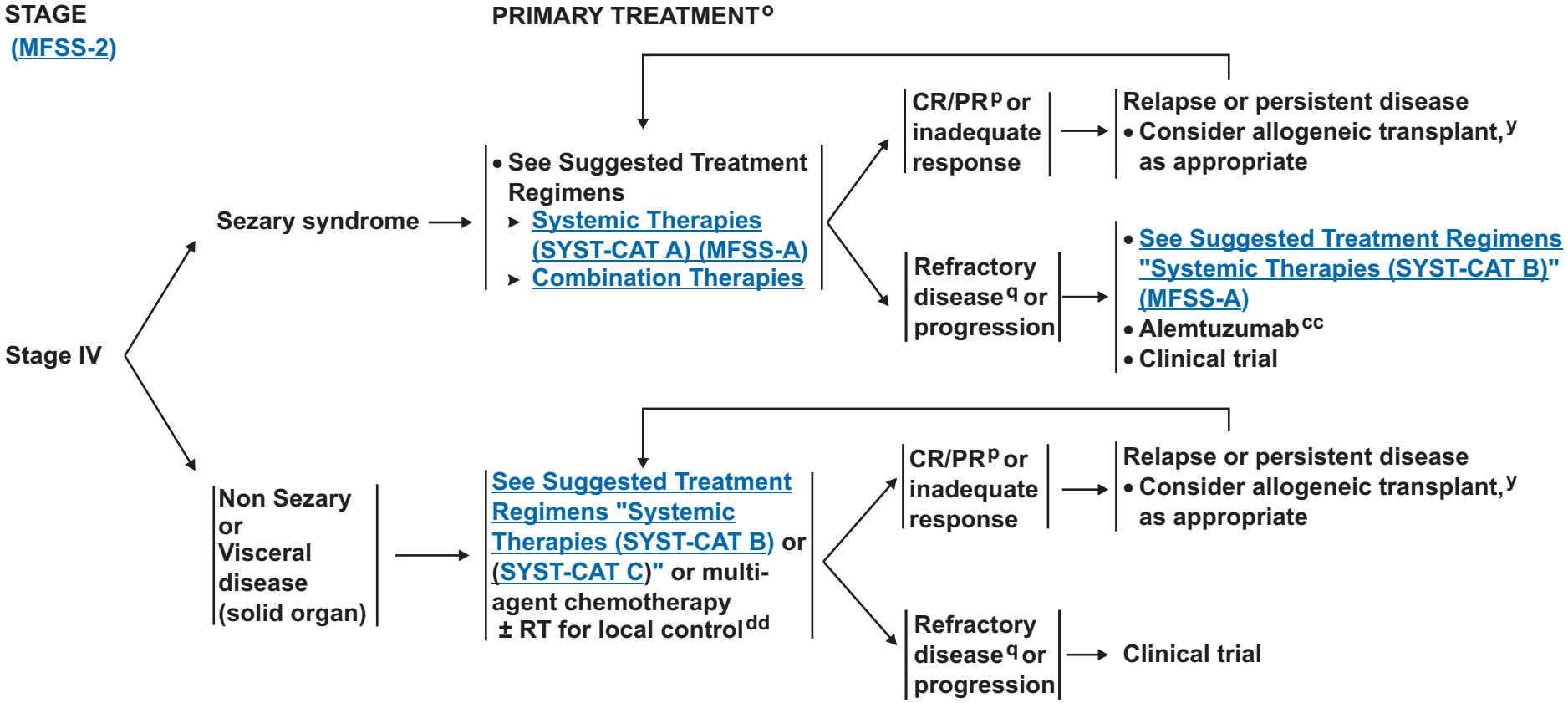
[bb] Combination therapy options can be considered earlier (primary treatment) depending on treatment availability or symptom severity.

[cc] Alemtuzumab can be administered by IV or subcutaneously. Lower doses administered subcutaneously have shown lower incidence of infectious complications.

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[o] It is preferred that treatment occur at centers with expertise in the management of the disease.

[p] Patients achieving a response 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.

[q] Refractory or intolerant to multiple previous therapies.

[y] The role of allogeneic HSCT is controversial. See discussion for further details.

[cc] Alemtuzumab can be administered by IV or subcutaneously. Lower doses administered subcutaneously has shown lower incidence of infectious complications.

[dd] 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 (nitrogen mustard, carmustine)
- Local radiation (particularly unilesional presentation, 24-36 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, carmustine)
- Phototherapy (UVB, nbUVB, for patch/thin plaques; PUVA for thicker plaques)[c]
- Total skin electron beam therapy (30-36 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]
- Denileukin diftitox
- 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)
  - Bortezomib
  - Low dose pralatrexate

SYSTEMIC THERAPIES (continued)

Category C (SYST-CAT C)
- Liposomal doxorubicin
- Gemcitabine
- Denileukin diftitox
- Romidepsin
- Low or standard dose pralatrexate
- See regimens listed on TCEL-B[g]

COMBINATION THERAPIES

Skin-directed + Systemic
- Phototherapy + retinoid[e]
- Phototherapy + IFN
- Phototherapy + photopheresis[f]
- Total skin electron beam + photopheresis[f]

Systemic + Systemic
- Retinoid + IFN
- Bexarotene + denileukin diftitox
- 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 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] Combination regimens are generally reserved for patients with relapsed/refratory or extracutaneous disease.

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SUGGESTED TREATMENT REGIMENS
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.

Local radiation

Wilson LD, Kacinski BM, Jones GW. Local superficial radiotherapy in the management of minimal stage IA cutaneous T-cell lymphoma (Mycosis Fungoides). International Journal of Radiation Oncology, Biology, Physics 1998;40:109-115.

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.

Phototherapy (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 UV A monotherapy. Arch Dermatol 2005;141:305-311.

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

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SUGGESTED TREATMENT REGIMENS
References

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.

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.

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.

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SUGGESTED TREATMENT REGIMENS
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Systemic therapies continued

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Skin-directed + Systemic

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DIAGNOSIS

ESSENTIAL:[a]
- HTLV-1 serology: ELISA and confirmatory Western Blot if ELISA is positive
- Peripheral blood smear analysis for atypical cells[b]
- Flow cytometry on peripheral blood[c]

USEFUL IN CERTAIN CIRCUMSTANCES:
- Biopsy of lymph nodes (excisional), skin biopsy, GI tract, or bone marrow biopsy[d] 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:[e,f] CD3, CD4, CD7, CD8, and CD25

→

WORKUP

ESSENTIAL:
- Complete history and physical examination-including complete skin exam
- CBC and blood smear: lymphocytosis (ALC > 4000/µL in adults) in acute and chronic subtypes
- 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

DIAGNOSTIC CATEGORY

see ATLL-A

See Primary Therapy Chronic/ Smoldering (ATLL-2)

See Primary Therapy Acute (ATLL-3)

See Primary Therapy Lymphoma (ATLL-3)

[a] The diagnosis of ATLL requires histopathology and immunophenotyping of tumor lesion, *or* morphology and immunophenotying of peripheral blood, *and/or* HTLV serology.

[b] 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 morphological variations can be encountered. Presence of ≥ 5% atypical cells by morphology in peripheral blood is required for diagnosis in the absence of other criteria.

[c] Presence of ≥ 5% T-lymphocytes with an abnormal immunophenotype in peripheral blood is required for diagnosis.

[d] Bone marrow involvement is an independent poor prognostic factor.

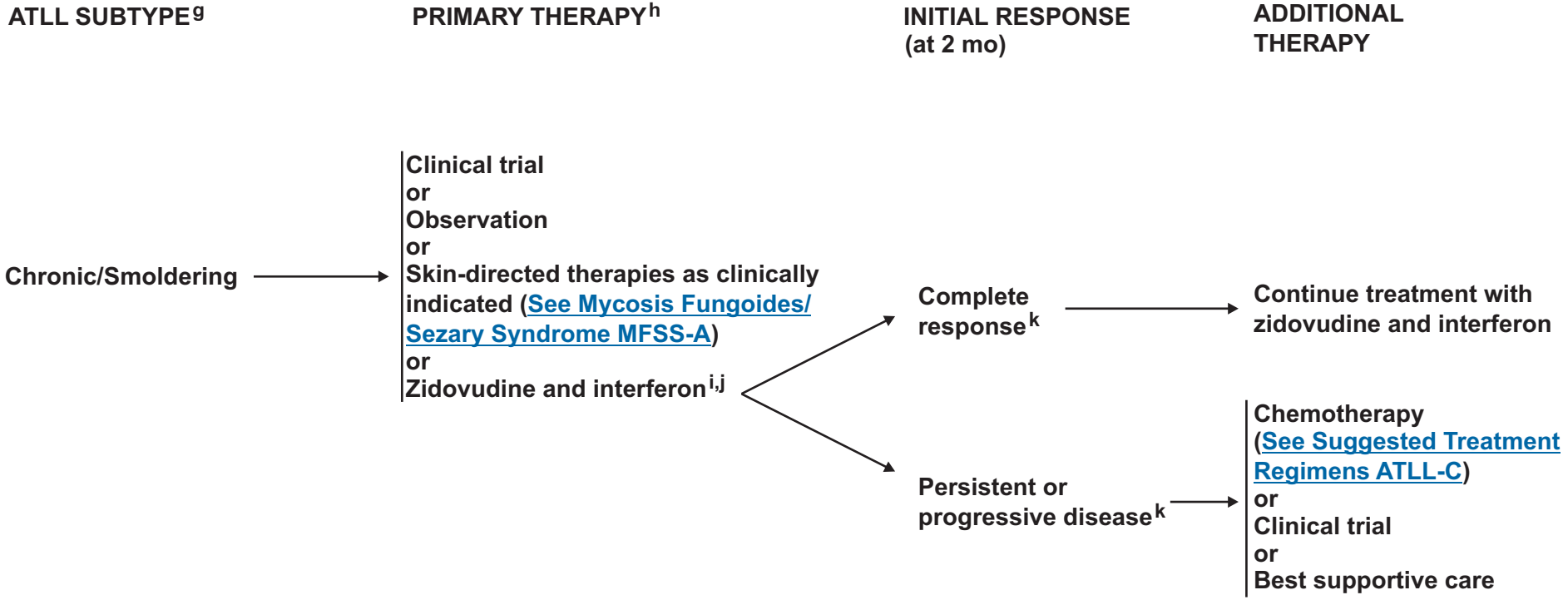
[e] See Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms (NHODG-A).

[f] 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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[g] See Diagnostic Criteria for Clinical Subtype of ATLL (ATLL-A).

[h] Supportive care: anti-infectious prophylaxis with sulfamethoxazole/trimethoprim + strongyloidosis prophylaxis is recommended.

[i] 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 two months period.

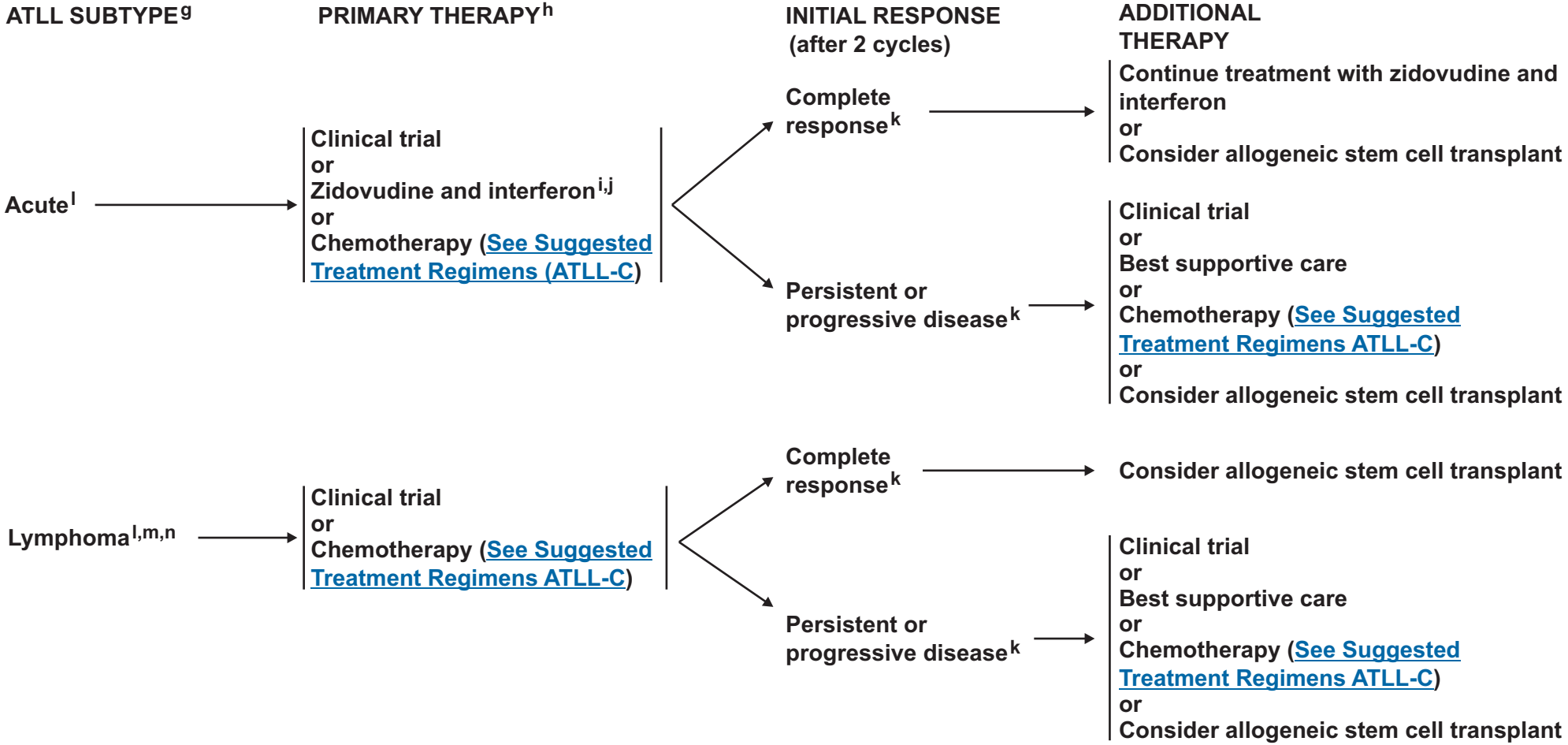
[j] See references for zidovudine and interferon (ATLL-D).

[k] See Response Criteria for ATLL (ATLL-B).

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[h] Supportive care: anti-infectious prophylaxis with sulfamethoxazole/trimethoprim + strongyloidosis prophylaxis is recommended.
[i] 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 two months period.
[j] See References for zidovudine and interferon (ATLL-D).
[k] See Response Criteria for ATLL (ATLL-B).
[l] Efficacy of long term treatment is limited. There are small series where transplant is beneficial. There is no defined treatment.
[m] Antiviral therapy is not effective.
[n] CNS prophylaxis: intrathecal chemotherapy is recommended (methotrexate and cytarabine and corticosteroids).

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DIAGNOSTIC CRITERIA AND CLASSIFICATION OF CLINICAL SUBTYPES OF ATLL[a]

	Healthy carrier	Smoldering ATL	Chronic ATL	Acute ATL	ATL Lymphoma
Anti-HTLV-1 serology	+	+	+	+	+
Clonal intergration of provirus	- (blood)	+ (blood)	+ (blood)	+ (blood)	+ (lymph nodes)
Lymphocyte count	Normal	Normal	Elevated	Elevated	Elevated
Abnormal cells (%)	< 5%	> 5%	> 5%	> 5%	< 1%
Hypercalcemia	-	-	-	+	+
LDH	Normal	≤ 1.5 N	≤ 2 N	> 2 N	> 2 N
Skin and lung involvement	-	+	+	+	+
Bone marrow or spleen involvement	-	-	+	+	+
Bone, GI or CNS involvement	-	-	-	+	+

[a] Modified from 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.

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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 to 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]**
  - **CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)**
  - **Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)**
  - **HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine**

[a]There is not 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, Panelatti G, Ramos JC, et al. A worldwide meta-analysis on the use of zidovudine and interferon-alpha for the treatment of adult T cell leukemia/lymphoma. ASH Annual Meeting Abstracts. 2007;110:2049.

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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 1.2011
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 non-diagnostic.**
- **A FNA or core needle biopsy alone is not suitable for the initial diagnosis of lymphoma.[b]**
- **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]**
  - **Recommended immunohistochemistry (IHC) panel: B cell: CD20; T lineage antigens: CD2, CD7, CD8, CD4, CD5. cCD3ε; NK lineage markers: CD56; Ki-67 (nuclear antigen marker)**
  - ***in situ* hybridization (ISH) for (EBER-1/2)[c]**

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[d]**
- **Chest/abdominal/pelvic CT with contrast of diagnostic quality or PET-CT scan with diagnostic quality CT**
- **Dedicated CT of the nasal cavity, hard palate, anterior fossa or MRI nasopharynx**
- **Calculation of NK/T-cell PI[e]**
- **MUGA scan/echocardiogram if treatment includes regimens containing anthracyclines or anthracenediones**
- **EBV viral load[f]**

USEFUL IN SELECTED CASES:

- **Pregnancy testing in women of child-bearing age**
- **Discussion of fertility and sperm banking**
- **HIV**

See Induction Therapy (NKTL-2)

[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.

[b] Typical NK/T-cell immunophenotype: CD20-, CD2+, cCD3ε+/Surface CD3 is usually absent, CD7+, CD8+ CD45RO+, CD43+, CD56+, T-cell receptor (TCR)αβ-, TCR-, TCRγδ, TCR and Ig genes are usually germline (NK lineage).

[c] Negative result should prompt pathology review for alternative diagnosis.

[d] BM aspirate - lymphoid aggregates rare, considered involved if EBER-1 positive, hemophagoctosis may be present.

[e] See NK/T-cell Lymphoma Prognostic Index (NKTL-A).

[f] 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.

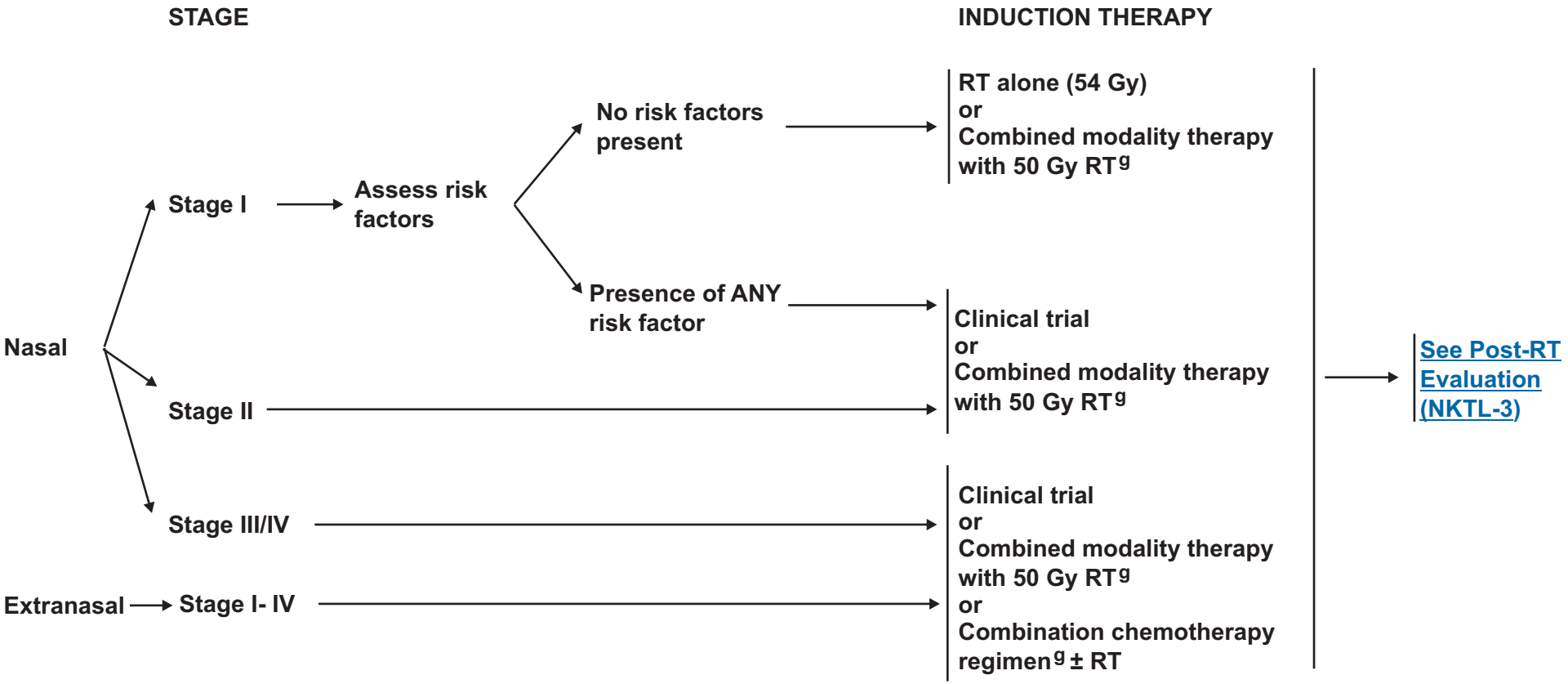
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Risk factors
(includes elements of NK/T-cell Lymphoma PI on NKTL-A)

- Age > 60 y
- B symptoms
- ECOG PS ≥ 2
- Elevated LDH
- Regional node involvement
- Local tumor invasion (LTI); bone or skin
- Histological evidence of high Ki-67 staining
- EBV DNA titer ≥ 6.1×10^7 copies/ml

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.

[g]L-asparaginase based chemotherapy (See Suggested Treatment Regimens NKTL-B).

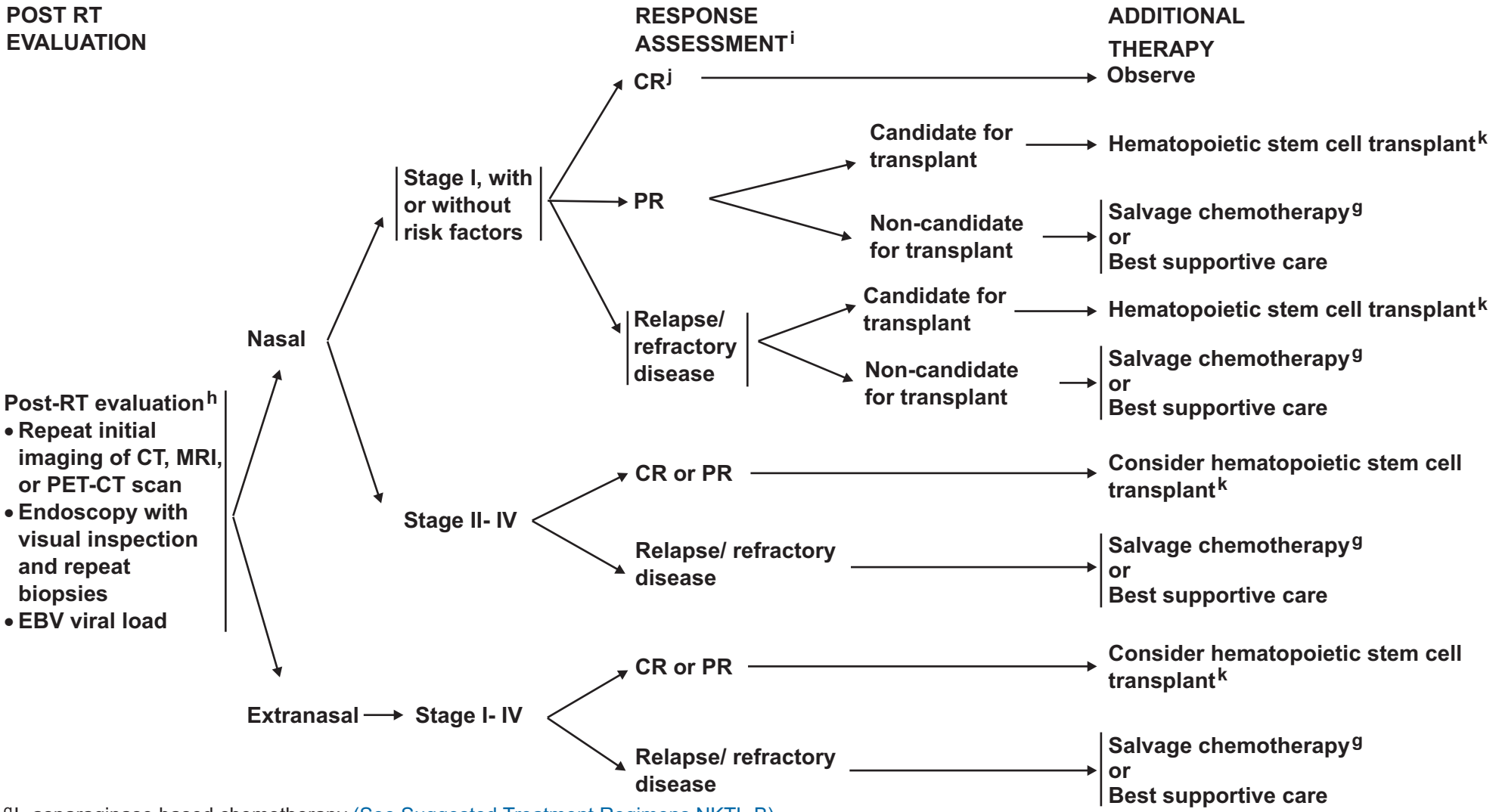
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[g] L-asparaginase based chemotherapy (See Suggested Treatment Regimens NKTL-B).
[h] The role of PET scan in this disease is not well established.
[i] See Response Criteria for Lymphoma (NHODG-C).
[j] Includes a negative ENT evaluation.
[k] Allogeneic preferred, if matched donor available.

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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NK/T CELL LYMPHOMA PROGNOSTIC INDEX[a]

ALL PATIENTS

Serum LDH > 1 x normal
B symptoms
Lymph nodes, N1 to N3, not M1
Ann Arbor Stage III

	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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SUGGESTED TREATMENT REGIMENS[a]

Radiotherapy alone

- **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. The recommended tumor dose was at least 54 Gy. Up-front RT may yield more benefits on survival in patients with Stage I disease.**

Combined Modality Therapy

- **Concurrent radiotherapy (50 Gy) and 3 courses of dexamethasone, etoposide, ifosfamide, and carboplatin (DeVIC)**
- **CCRT (ie radiation 40 to 52.8 Gy and cisplatin 30 mg/m^2 weekly). Three cycles of VIPD (etoposide 100 mg/m^2 days 1 through 3, ifosfamide 1,200 mg/m^2 days 1 through 3, cisplatin 33 mg/m^2 days 1 through 3, and dexamethasone 40 mg days 1 through 4) were scheduled after CCRT.**

Combination chemotherapy regimen (L-asparaginase based)

- **SMILE (steroid [dexamethasone], methotrexate, ifosfamide, L-asparaginase, and etoposide)**

[a] See references for regimens NKTL-B 2 of 2.

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SUGGESTED TREATMENT REGIMENS

References

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.

Combined modality therapy
Yamaguchi M TK, Oguchi M, Isobe Y, et al, Japan Clinical Oncology Group Lymphoma Study Group (JCOG-LSG) Phase I/II study of concurrent chemoradiotherapy for localized nasal NK/T-cell lymphoma: Final results of JCOG0211. J Clin Oncol (Meeting Abstract). 2009;27:8549.
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.

Combination chemotherapy regimen (L-asparaginase based)
Jaccard A GN, Coppo P, Morschhauser F, et al. A prospective phase II trial of an L-asparaginase containing regimen in patients with refractory or relapsing extra nodal NK/T-cell lymphoma. ASH Annual Meeting Abstracts. 2008;112:79.
Yamaguchi M KY, Maeda Y, Hashimoto C, et al and The NK-Cell Tumor Study Group Phase II study of SMILE chemotherapy for newly-diagnosed stage IV, relapsed or refractory extranodal NK/T-cell lymphoma, nasal type: NKTSG study. J Clin Oncol (Meeting Abstract). 2010;28:8044.

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NCCN Guidelines™ Version 1.2011
Post-Transplant Lymphoproliferative Disorder

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DIAGNOSIS

ESSENTIAL:

- **Histopathology and adequate immunophenotype to establish diagnosis. Rebiopsy if consult material is nondiagnostic.**
  - ➤ **Recommended panel for paraffin section immunohistochemistry: CD3, CD5, CD10, BCL6, BCL2, IRF4/MUM1, CD20, CD79a, PAX5, Ki67**
  - ➤ **Cell surface marker analysis by flow cytometry: CD3, CD5, CD7, CD4, CD8, CD19, CD20, CD10, Kappa, lambda**
- **Epstein-Barr virus (EBER-ISH). If the less sensitive EBV-LMP1 stain is positive, EBER in situ hybridization is not required.**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **Panel for paraffin section immunohistochemistry: 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 genetic analysis to detect gene rearrangements: IgH by PCR**
- **BCL6 gene mutation analysis[a]**

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**
- **EBV PCR, CMV PCR**
- **Brain MRI**

→ **Early lesions**
→ **Polymorphic**
→ **Monomorphic**
→ **Classic Hodgkin lymphoma**

→ **See Primary Treatment (PTLD-2)**

[a] BCL6 gene mutation 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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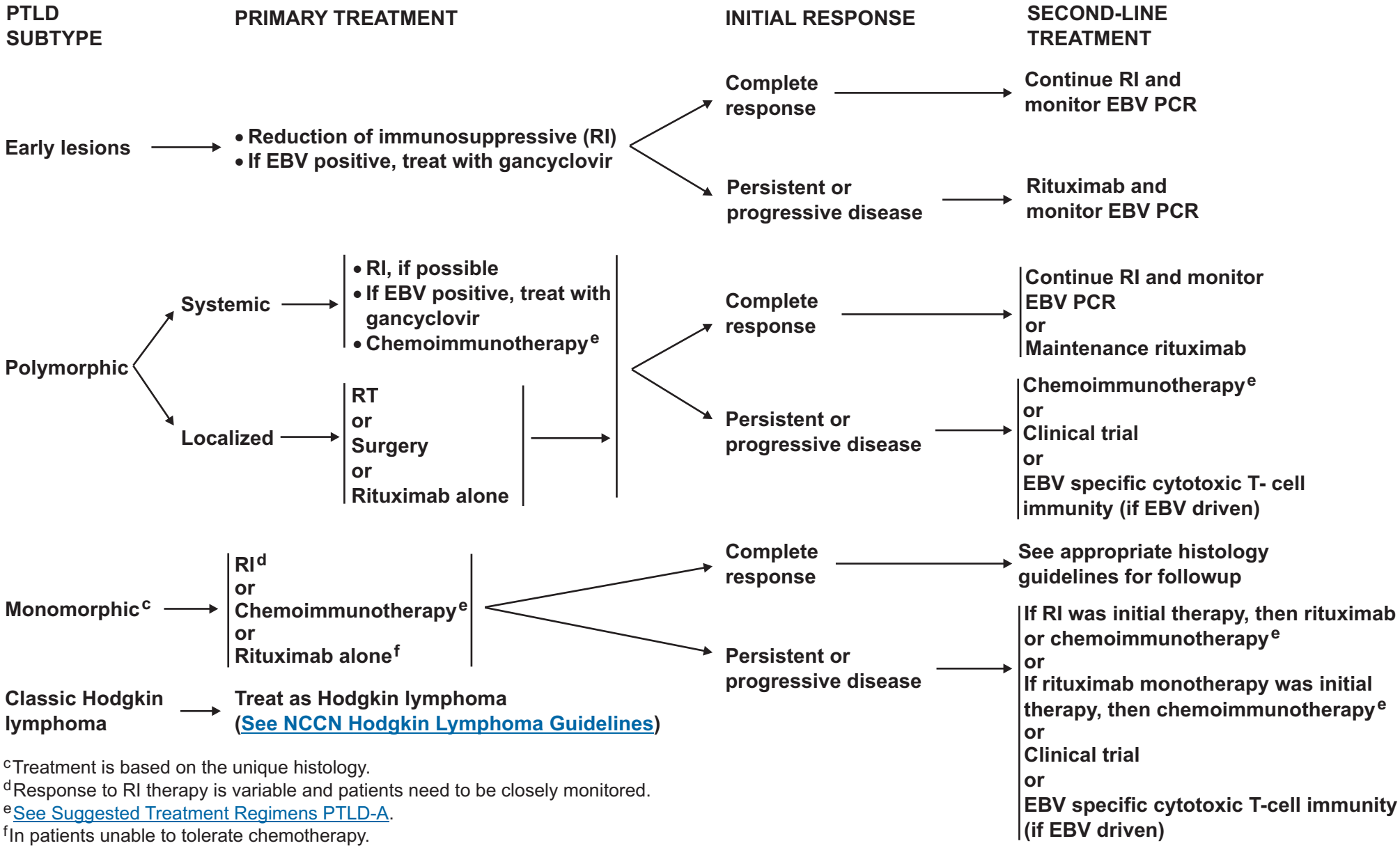
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[c] Treatment is based on the unique histology.
[d] Response to RI therapy is variable and patients need to be closely monitored.
[e] See Suggested Treatment Regimens PTLD-A.
[f] In patients unable to tolerate chemotherapy.

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SUGGESTED TREATMENT REGIMENS
(in alphabetical order)

RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)

RCHOEP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, etoposide)

RCVP (rituximab, cyclophosphamide, vincristine, prednisone) (for frail patients who cannot tolerate anthracycline)

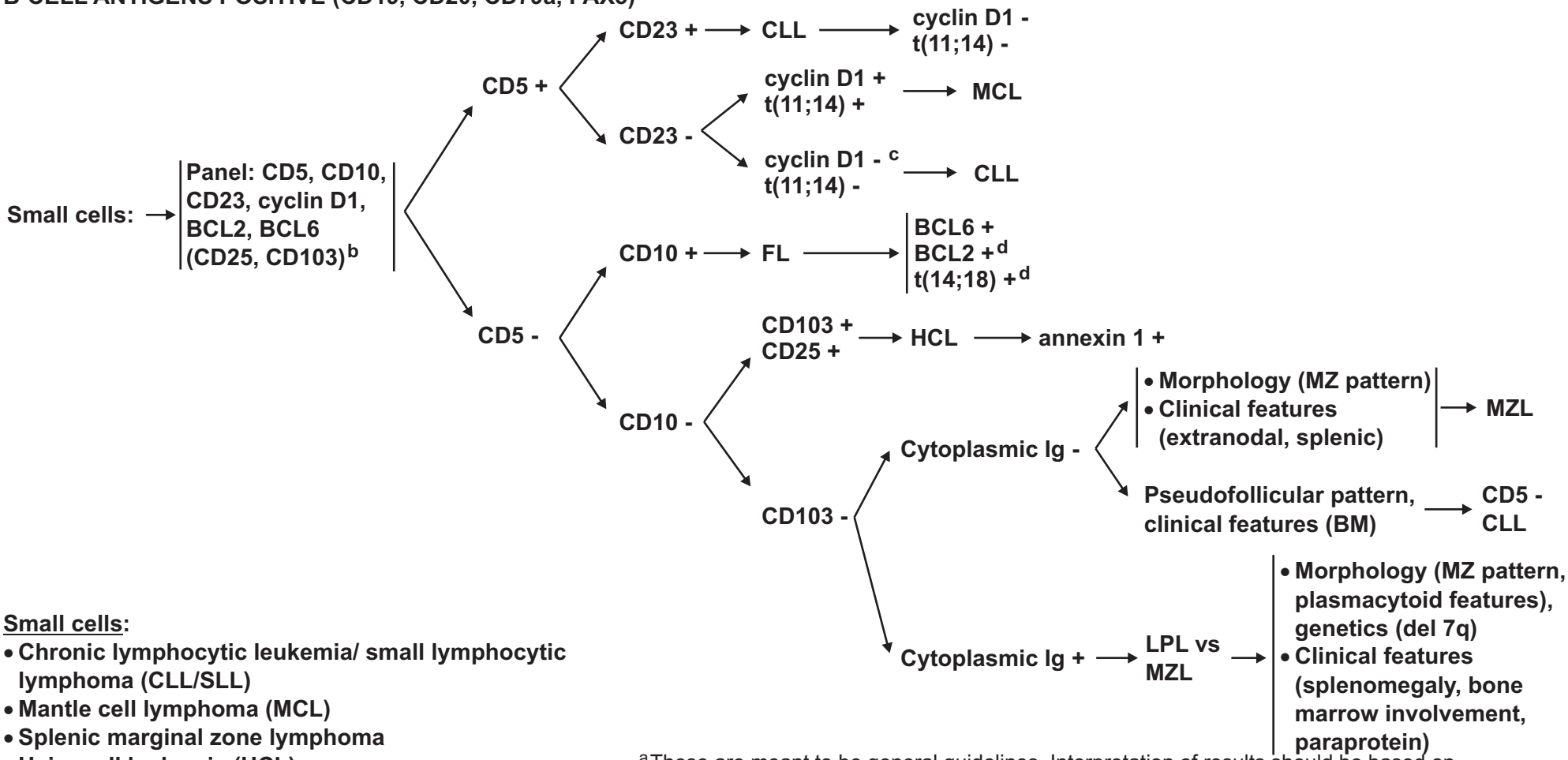
See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)

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USE OF IMMUNOPHENOTYPING/GENETIC TESTING IN DIFFERENTIAL DIAGNOSIS OF MATURE B-CELL AND T/NK-CELL NEOPLASMS[a]
(TO BE USED IN CONJUNCTION WITH CLINICAL PATHOLOGICAL CORRELATION)

B-CELL ANTIGENS POSITIVE (CD19, CD20, CD79a, PAX5)



Small cells:

- Chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/SLL)
- Mantle cell lymphoma (MCL)
- Splenic marginal zone lymphoma
- Hairy cell leukemia (HCL)
- Lymphoplasmacytic lymphoma (LPL)
- Extranodal marginal zone lymphoma (MALT lymphoma)
- Nodal marginal zone lymphoma
- 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.
[b] Flow cytometry, blood or bone marrow, if HCL is in differential diagnosis.
[c] Rare cases of both cyclin D1 and t(11;14) negative MCL have been reported. This diagnosis should be made with extreme caution and with expert consultation.
[d] 85% of Follicular Lymphoma will be BCL2 + or t(14;18) +.

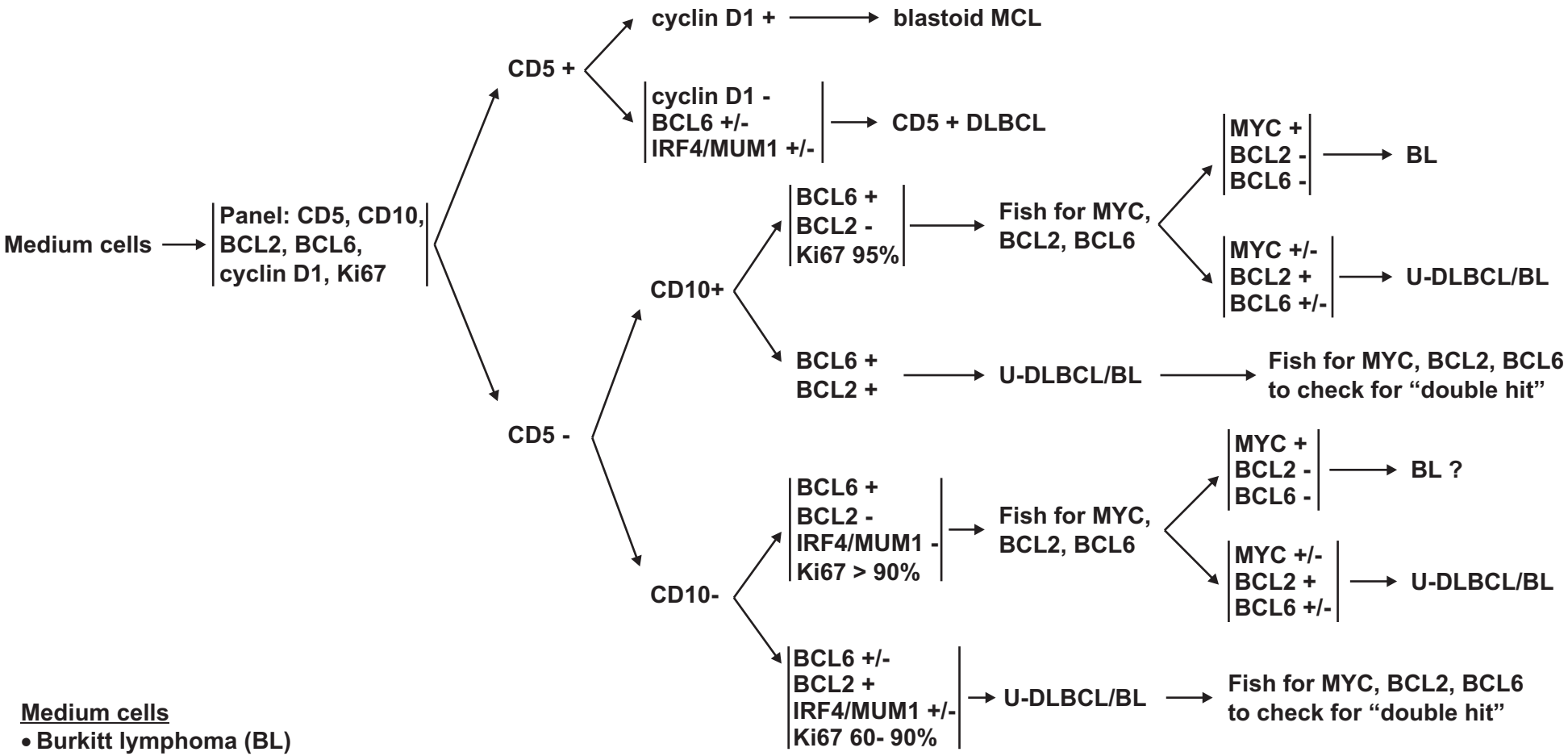
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B-CELL ANTIGENS POSITIVE (CD19, CD20, CD79a, PAX5)



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)**

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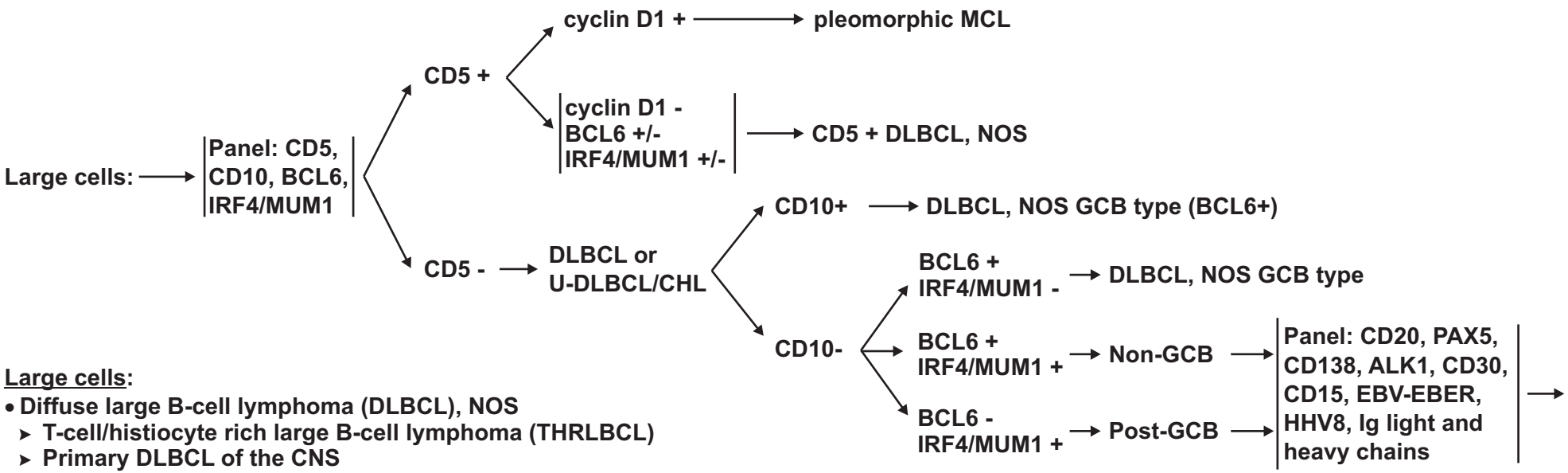
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(TO BE USED IN CONJUNCTION WITH CLINICAL PATHOLOGICAL CORRELATION)

B-CELL ANTIGENS POSITIVE (CD19, CD20, CD79a, PAX5)



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**

Continued on next page

GCB= Germinal center B-cell like

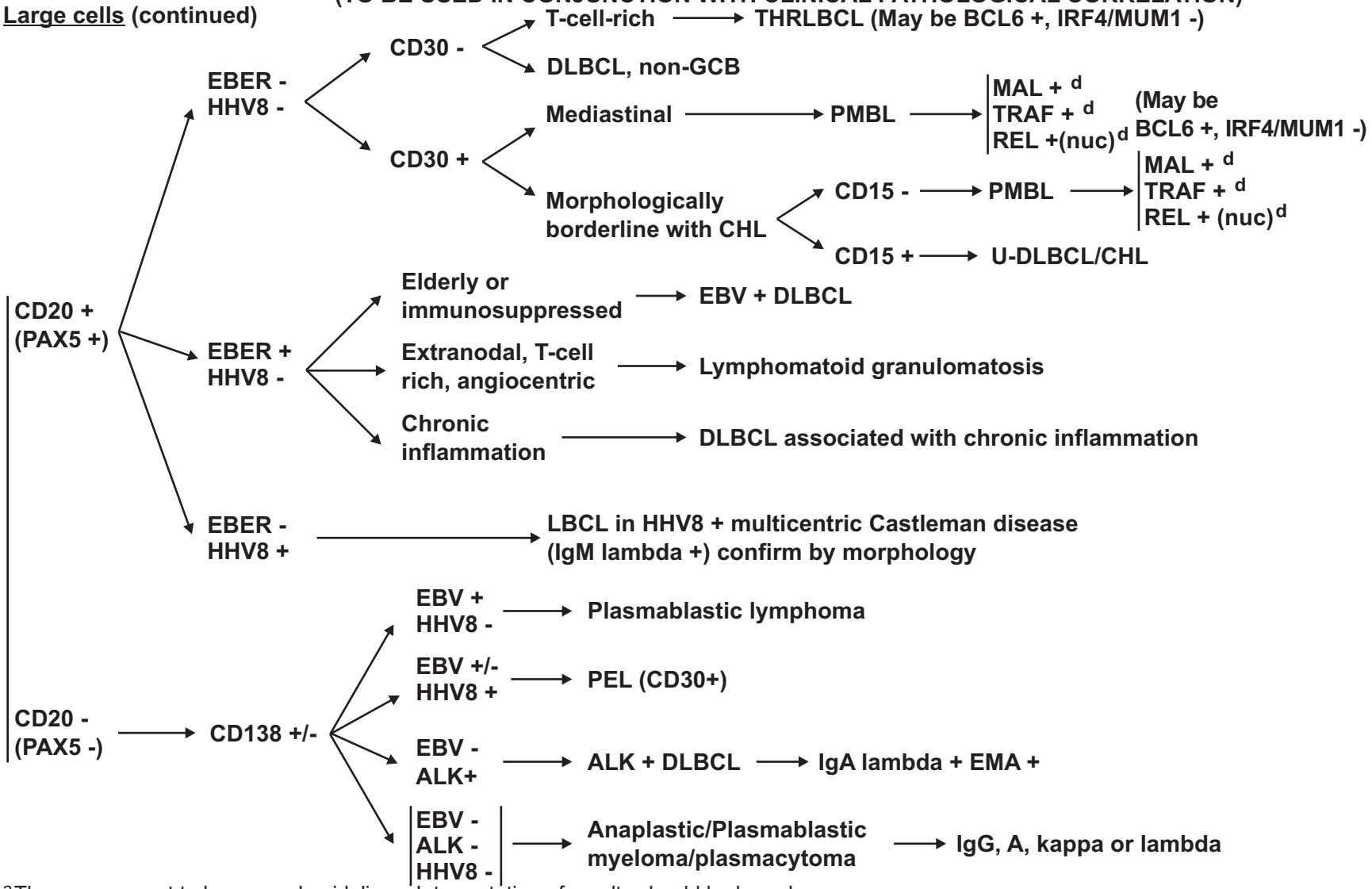
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[d] These stains/studies are not routinely available.

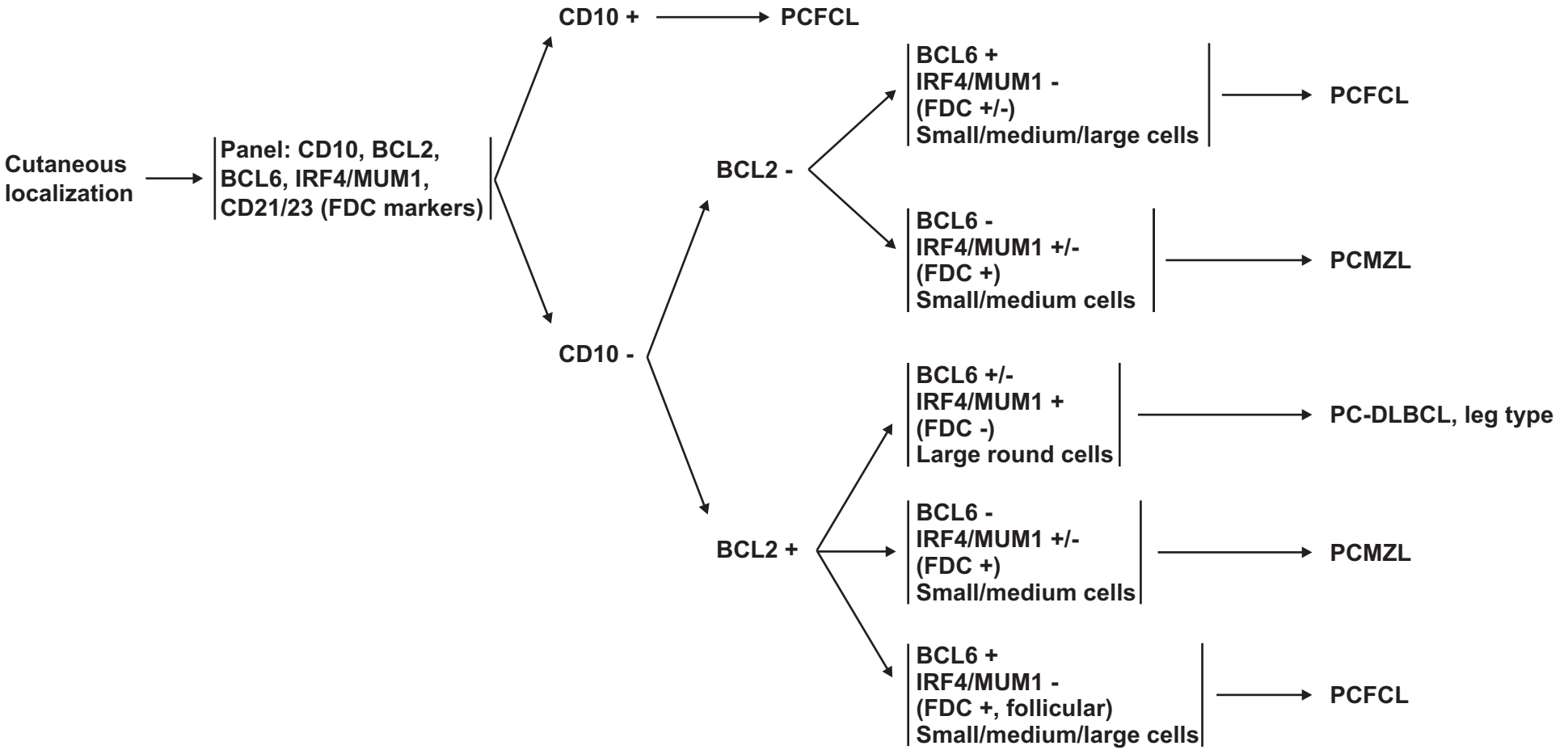
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(TO BE USED IN CONJUNCTION WITH CLINICAL PATHOLOGICAL CORRELATION)

B-CELL ANTIGENS POSITIVE (CD19, CD20, CD79a, PAX5)



- **Primary cutaneous marginal zone lymphoma (PCMZL)**
- **Primary cutaneous follicle center lymphoma (PCFCL)**
- **Primary cutaneous DLBCL, leg type (PC-DLBCL, leg type)**

FDC = Follicular dendritic cells

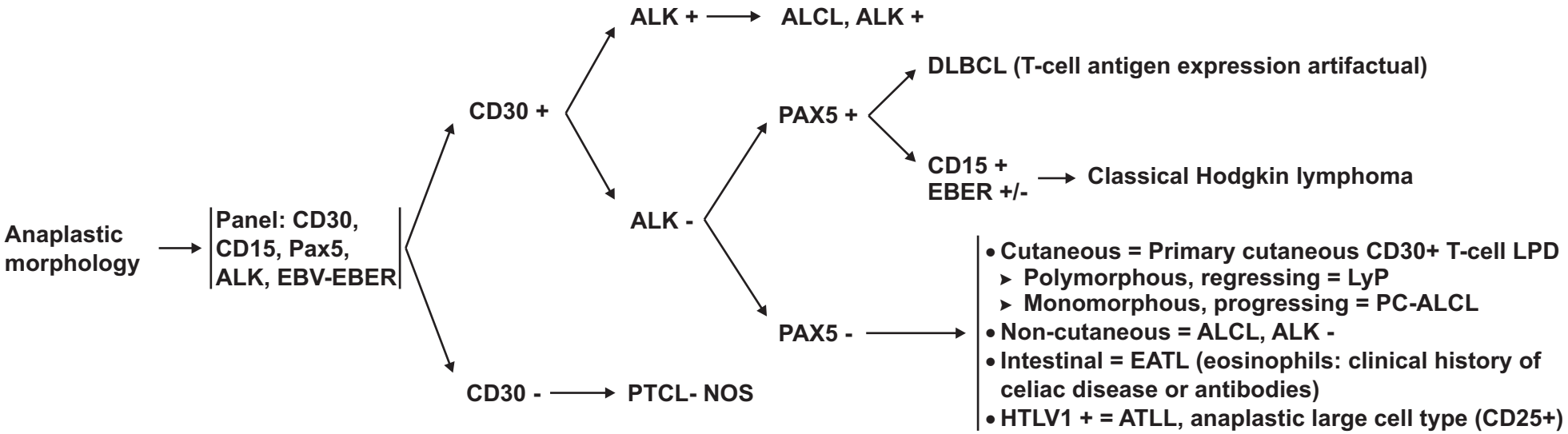
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(TO BE USED IN CONJUNCTION WITH CLINICAL PATHOLOGICAL CORRELATION)
T-CELL ANTIGENS POSITIVE (CD2, CD3, CD5, CD7) [and B-cell antigens negative]



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.

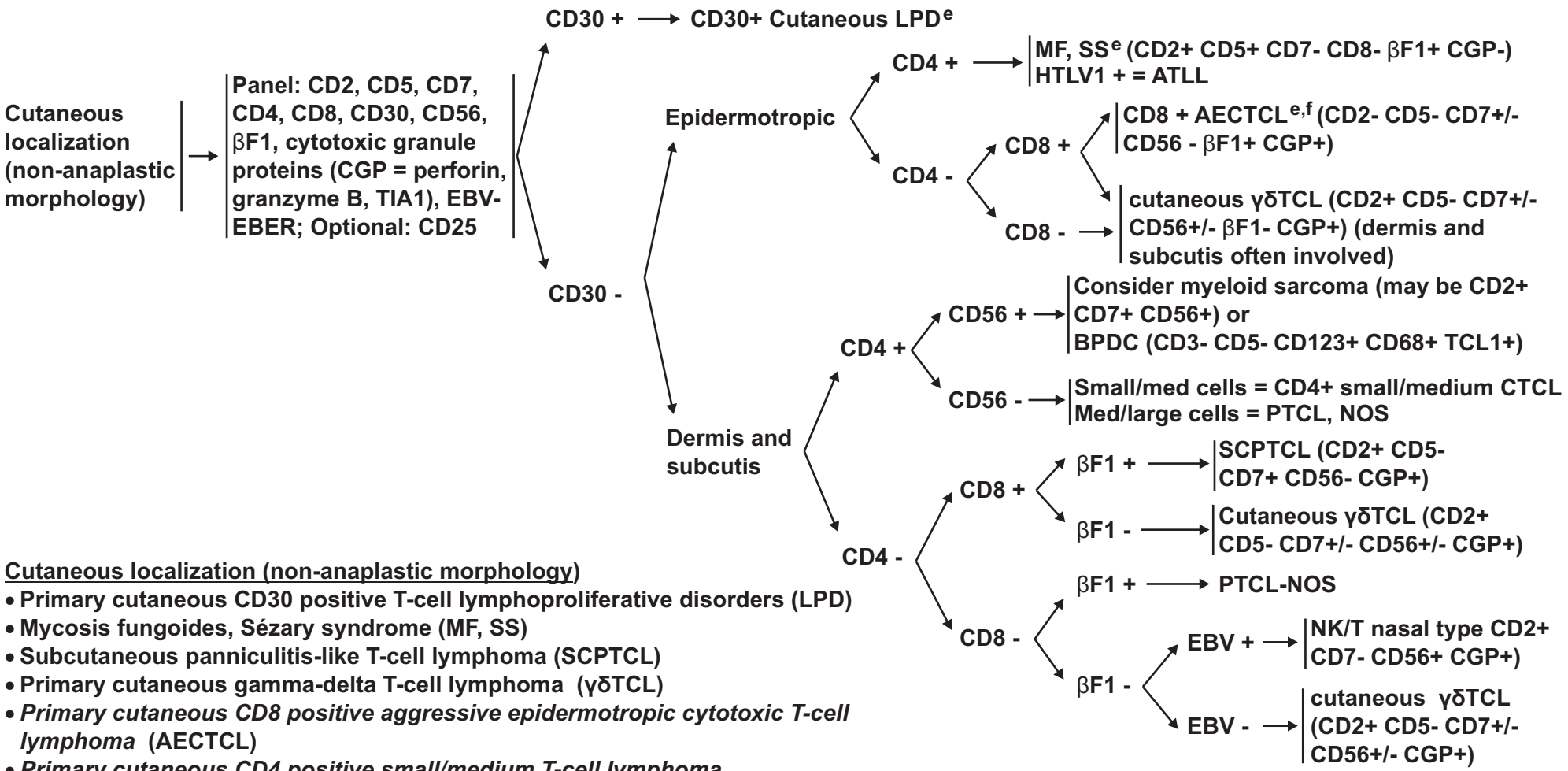
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(TO BE USED IN CONJUNCTION WITH CLINICAL PATHOLOGICAL CORRELATION)

T-CELL ANTIGENS POSITIVE (CD2, CD3, CD5, CD7) [and B-cell antigens negative (Pax5)]



<u>Cutaneous localization (non-anaplastic morphology)</u>

- 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 neoplasm (BPDC)

[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]A minority of MF cases can be CD30+, CD4 - and either CD8 +/-, TIA1 +.
[f]AECTCL has distinctive morphology and clinical presentation.

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Extranodal, noncutaneous localization (non-anaplastic morphology) → **Panel: ALK1, CD5, CD7, CD4, CD8, CD30, C56, βF1, cytotoxic granule proteins (CGP = perforin, granzyme B, TIA1), EBV-EBER**

- **EBER +** → **ENK/TCL (CD5- CD4- CD8- CD30- CD56+ CGP+, midline face, upper aerodigestive tract, testis, GI tract)**
- **EBER -**
  - **CD30 +**
    - **ALK +** → **ALCL, ALK+ small cell or histiocyte-rich variants**
    - **ALK -** →
      - **Intestinal, other abdominal/visceral sites, celiac disease or markers positive = EATL (CD 5- CD7- CD4- CD8-/+ CD56-/+ TIA1+ GRB+ Perf+)**
      - **Other sites, celiac disease markers negative = PTCL, NOS**
  - **CD30 -** →
    - **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: CD5, CD4, CD8, CD30, ALK1, CD10, BCL6, PD1, CD21, CD23, EBV-EBER**

- **CD30 + ALK +** → **ALCL, ALK+ small cell or histiocyte-rich variants**
- **CD30 +/- ALK -**
  - **CD10 + BCL6 + PD1 + CD4 +/-** →
    - **Vascular proliferation, expanded CD21+ CD23+ FDC = AITL**
    - **Nodular CD21+ CD23+ FDC = Nodular PTCL**
  - **CD10 - BCL6 -**
    - **HTLV1 + = ATLL (CD2+ CD5+ CD7- CD 25+ 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**

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TUMOR LYSIS SYNDROME

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. 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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RESPONSE CRITERIA FOR 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

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REVISED RESPONSE CRITERIA FOR 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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MONOCLONAL ANTIBODY DIRECTED AT CD20 AND VIRAL REACTIVATION

- **Hepatitis B surface antigen (HBSAg) and Hepatitis B core antibody (HBCAb) testing for all patients receiving rituximab**
  - **Quantitative hepatitis B viral load by PCR only if one of the screening tests positive**
  - **In areas with high prevalence/ population or prevalence is HBV not known, recommend testing all patients receiving immunotherapy, chemotherapy, or chemoimmunotherapy**

Note: Patients receiving IV immunoglobin may be HBCAb positive as a consequence of IVIG therapy.

- **Empiric antiviral therapy with oncologic treatment for any patient who is HBSAg or HBCAb positive**
  - **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, consult hepatologist**
  - **Maintain prophylaxis for at least 6 months after oncologic treatment ends**
    - **Consult with hepatologist for duration of therapy in patient with active hepatitis B virus**

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 treatments**
- **Check for 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.
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PRINCIPLES OF RADIATION THERAPY[a]

Field:
Options: Involved-Field or Reduced Involved-Field

For extra nodal sites:
- **Organ involvement: The field includes the involved organ alone (example: Gastric MALT- the whole stomach; Parotid- the total unilateral parotid gland).**
- **Bone/spine involvement: Only the involved part of the organ is irradiated (with margins). No radiation is required to uninvolved adjacent lymph nodes.**

For nodal sites:
- **Field: In most cases an involved-field is appropriate. Regional fields or extended-field are not recommended unless there is significant concern that adjacent nodes are involved.**
  - **In DLBCL, RT consolidation following chemotherapy, RT may be limited to the originally involved lymph node(s). In the mediastinum, abdomen and pelvis treating only the post-chemotherapy volume in the transverse diameter is recommended.**
  - **When RT is the primary treatment, involved-field or reduced-IFRT (involved nodal radiation therapy) is recommended.**
  - **Margins are influenced by the quality of imaging and clinical information.**

Dose:
- **RT for follicular lymphoma: 24-30 Gy (36 only if bulky)**
- **RT for MALT lymphoma: Stomach- 30 Gy. Other organs 24-30 Gy**
- **RT for early stage mantle cell lymphoma: 30-36 Gy**
- **Consolidation dose in DLBCL following CR to chemotherapy: 30-36 Gy**
  - **RT dose for residual disease (PR) after chemotherapy: 40-50 Gy.**
- **Mini-RT for palliation of advanced-stage low-grade lymphomas (FL, SLL, MZL, MCL): 2 GyX2 (may be repeated)**

[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.

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.

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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 macroglobinemia
- 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

Continued on next page

*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 vaccineforme-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-Tranplant 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#

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 Press: 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 of Clin Onc* 1989;7(11): 1630-1636.

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Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 10/04/08

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of lymphoproliferative disorders originating in B-lymphocytes, T-lymphocytes or natural killer (NK) lymphocytes. In the United States, B-cell lymphomas represent 80-85% of the cases with 15-20% being T-cell lymphomas. NK lymphomas are very rare. An estimated 66,120 new cases of NHL will be diagnosed in 2008 and 19,160 deaths will occur. NHL is the fifth leading site of new cancer cases among men and women, accounting for 4-5% of new cancer cases and 3% of cancer-related deaths. NHL is also the ninth leading cause of cancer deaths among men and the sixth among women.[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.

Classification

The International Working Formulation (IWF) classified NHL into three major categories as low, intermediate and high grade, based on the morphology and natural history. The Revised European-American Classification of Lymphoid neoplasms (REAL) was developed in 1994, which classified based the classification on cell of origin (B, T, or NK) and included morphology, immunophenotype, genetic and clinical features.[3] The currently internationally accepted World Health Organization (WHO) classification is a refinement of the REAL classification (ST-1).[4]

The REAL/WHO classification of NHL includes several additional, newly identified entities not recognized by the IWF.[4] 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 and genetic features. These considerations have aided in defining active treatment for specific subtypes of lymphoma.

Discussion update in progress

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Currently, a comprehensive description of the natural history and clinical features of all NHL diagnoses recognized by the WHO classification does not exist. However, the International Lymphoma Classification Project evaluated 1,403 lymphoma cases and identified the thirteen most common histologic types, comprising about 90% of the cases of NHL in the United States.[5] The findings were as follows: diffuse large B-cell (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 marginal zone B-cell lymphoma (MZL), mucosa-associated lymphoid tissue (MALT) lymphoma, 5%. The remaining subtypes each occurred in less than 2% of cases. Composite lymphomas were not included in these distribution figures. Importantly, in the United States more than 50% of cases of lymphoma are either DLBCL or FL. In a study performed by the International T-cell Lymphoma Project, PTCL-not otherwise specified (PTCL-NOS) was the most common subtype of PTCL (29.3%).[6]

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 measured by CT scan and the extent of bone marrow involvement that is determined by bone marrow aspirate and biopsy.[7] These guidelines were revised in 2007 by the International Harmonization Project to incorporate immunohistochemistry (IHC) flow cytometry and 18-flouro-deoxyglucose (FDG)-positron emission tomography (PET) scans in the definition of response for lymphoma.[8] 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. Response criteria for lymphoma are summarized in NHODG-C.

NCCN Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines were developed for the most common subtypes of NHL:

B-cell lymphomas:

Indolent lymphomas

- Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)
- Follicular lymphoma
- Marginal Zone Lymphoma
  - MALT Lymphoma
  - Splenic MZL
  - Nodal MZL

Aggressive lymphomas

- Diffuse large B-cell lymphoma
- Mantle cell lymphoma

Highly aggressive lymphomas

- Burkitt lymphoma
- Lymphoblastic lymphoma
- AIDS-related B-cell lymphoma

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T-cell lymphomas:

- Peripheral T-cell lymphoma
- Mycosis fungoides/Sezary syndrome

B-cell Lymphomas

Diagnosis

In all cases, the most important first step is to make an accurate pathologic diagnosis. The basic pathological evaluation is the same in each guideline though some further evaluation may be useful in certain circumstances to clarify a particular diagnosis; these are outlined in the pathological evaluation of the individual guideline.

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.[9,10] 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 obviate the need for a more invasive biopsy. Recent studies have shown that the diagnostic accuracy of FNA improves significantly when it is used in combination with immunohistochemistry, flow cytometry or excisional biopsy.[11,12,13]

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 excisional or incisional biopsy and flow cytometry may provide better information to provide a 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, proper diagnosis and choice of treatment for each subtype. It can be performed by flow cytometry and/or immunohistochemistry; the choice depends on the antigens as well as the expertise and resources available to the hematopathologist. In some cases flow cytometry and immunohistochemistry are complementary diagnostic tools.[14] Molecular cytogenetic analysis may be necessary under certain circumstances to identify the specific chromosomal translocations that are more commonly seen in particular NHL subtypes.

Dysregulated expression of cyclin D1 is a cell-cycle protein that results from the chromosomal translocation, t(11;14) seen in the vast majority of cases of MCL. This translocation is not seen in other NHLs though can be seen in multiple myeloma (MM). Cyclin D1 expression is the most reliable marker for differentiating between CLL and MCL. Thus, Cyclin D1 immunohistochemistry or cytogenetic analysis with fluorescent *in* situ hybridization (FISH) for t(11;14) should be considered for cases of CLL with atypical immunophenotype (CD 23 dim or negative). Analysis of cyclin D1 is helpful in confirming the diagnosis when morphology suggests MCL, though the immunophenotype demonstrates expression of CD 23 positive. BCL2 is over-expressed as the consequence of the t(14;18) translocation seen in 90% of cases of FL and about 20% of cases of DLBCL. However, BCL2 expression is commonly seen in other lymphoma and cannot be used reliably to establish the diagnosis of FL. CD10 expression is useful in differentiating FL from MZL.

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The monoclonal antibody Ki-67 is used to detect proliferation index (PI) which has been found to have prognostic significance in FL as well as in other lymphomas. The Southwest Oncology Group (SWOG) trial evaluated the utility of Ki-67 for predicting survival in patients with aggressive NHL.[15] Overall survival (OS) was significantly reduced in patients with high Ki-67 (high PI) compared to those lower PI. Estimated one-year survival was found to be 18% (high PI) compared to 82% for those with low PI. In two other reports, disease-specific survival was significantly better in patients who had FL with a low PI as determined by the staining of Ki-67.[16,17] Immunohistochemical staining with Ki-67 may be useful in the histological grading of FL.[18] Higher grade follicular lymphomas had greater number of Ki-67 cells.

Work-up

Essential work-up 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 testing (see below), chest/abdominal/pelvic CT, and comprehensive metabolic panel. 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).

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 ought to be performed under certain circumstances.[19]

Hepatitis B reactivation has been reported in several patients treated with rituximab in combination with chemotherapy. In some cases viral infections occurred up to one year following discontinuation of rituximab. Due the risk of hepatitis B reactivation, the panel has included hepatitis B testing as part of essential work-up prior to initiation of treatment in all patients who will receive rituximab. However, hepatitis B reactivation has also been seen with chemotherapy alone and any patient with risk factors (including history of blood transfusion) should be evaluated. Hepatitis B testing should include surface antigen/antibody and core antigen/antibody. Antiviral prophylaxis may be beneficial in preventing hepatitis B reactivation.[20] Hepatitis C testing is needed only in high-risk patients.

Bone marrow biopsy is usually included in the work-up for all patients with NHL. 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.[21] In a recent 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. 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.[22] The effect of bone marrow biopsy on the management of patients or on the prognosis of lymphoma has not been proven in prospective clinical trials.

In the NCCN guidelines, bone marrow biopsy with or without aspirate is included as part of essential work-up for all lymphomas. However, in the case of patients with low bulk indolent disease with radiographic clinical stage III disease, an initial staging bone marrow evaluation can be deferred if immediate treatment will not be offered as it will not

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change the clinical recommendations. However, in early stage FL, bone marrow biopsy and aspirate is essential. Unilateral or bilateral core biopsy can be used.[23] Bilateral cores are recommended if radioimmunotherapy is considered.

PET scan has been used for initial staging, restaging and follow-up of patients with NHL.[24] In a recent meta-analysis, PET showed a high positivity and specificity when used for the staging and restaging of patients with lymphoma.[25] However, PET scans can be misleading since other organs in addition to the malignant tumors can take up radioactive FDG. Lesions smaller than 1 cm are not reliably visualized with PET scans. PET scan is currently not used routinely for staging in lymphoma because PET scans detect additional disease sites with the modification of clinical stage only in 15-20% of patients; the impact on therapy was even less frequent at 8%. PET scan has generally been used in conjunction with a diagnostic CT scans.

Integrated PET-CT is a new imaging technology that has distinct advantages in both staging and restaging compared to full-dose diagnostic CT or PET alone.[26,27] 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 non-Hodgkin lymphoma.[26] 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.[27] 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 the role of PET-CT scans in the initial staging of lymphomas. The panel has included PET-CT scan as an optional work-up procedure for selected patients.

Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

Diagnosis

Chronic lymphocytic leukemia and small lymphocytic lymphoma (CLL/SLL) are different manifestations of the same disease and are managed in much the same way. The diagnosis of SLL is typically applied if the presentation is predominantly nodal and the diagnosis of CLL is made when the principal involvement is bone marrow and blood; however, classification of mixed cases is often arbitrary and the designation SLL/CLL recognizes this fact. As with all the lymphoid neoplasms, adequate hematopathologic review is essential to establish an accurate diagnosis of CLL/SLL. Additional paraffin-embedded material may be used for immunophenotyping to determine lineage and clonality.

Standard paraffin panel of immunohistochemical studies includes a Pan B-cell and a Pan T-cell marker to distinguish B-cell and T-cell malignancies. Immunohistochemical reagents can detect CD3, CD5, CD10, CD20, CD23 and cyclin D1. These can be useful, particularly for diagnosing CLL/ SLL type without circulating cells. Flow cytometric studies performed on patients with leukemic cell burden include kappa/lambda to access clonality. The typical immunophenotype in CLL/SLL is CD5+, CD10-, CD19+, CD20, dim expression of surface immunoglobulin, CD23+, CD43+/-, and cyclin D1-. Distinguishing CLL/SLL from MCL is essential, as they are both CD5+ B-cell tumors. Though CD23 is often helpful, cyclin D1- is critical in this differentiation of tumor types.

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There are important genetic determinants of prognosis in of SLL/CLL. Mutation of the immunoglobulin variable region (IgV_H) is associated with a favorable outcome. CD38 expression and zeta-associated protein 70 (ZAP-70) expression have been reported to inversely correlate with mutation status and therefore are predictors of clinical outcome in patients with CLL.[28, 29,30] Evaluation of ZAP-70 expression can be challenging and it should only be used if it has been shown to correlate with mutation status. Furthermore, chromosomal aberrations have important prognostic significance. FISH for detection of t(11:14), t(11q;v), del 13q, trisomy 12 and del17p (p53 gene deletions) can be performed on paraffin-embedded or fresh tissue. FISH for the t(11;14) chromosomal translocation can help distinguish MCL from CLL. Del17p is associated with short progression free survival (PFS) and predicts resistance to chemotherapy. The genetic lesions can evolve over time and therefore FISH analysis should be repeated prior to each treatment.

Staging

The Ann Arbor staging system has proven to be of limited utility in CLL because patients universally have bone marrow and peripheral blood involvement. In rare instances, patients may have nodal-only presentations of SLL. Two different staging systems, Rai and Binet system are currently used worldwide. The modified Rai classification is most useful clinically and provides important prognostic information.[31] Survival of patients with good-risk disease (Rai stage 0) is essentially the same as the survival rate of age-matched controls. Patients with intermediate-risk disease (Rai stage I-II) 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) have a poor prognosis. Binet staging system is based on the number of involved areas and the level of hemoglobin and platelets and like the Rai system has a good correlation with clinical outcome.

Workup

The workup for CLL/SLL is similar to the workup for other lymphoid neoplasms. Quantitative immunoglobulins may be particularly informative in patients with recurrent infections. 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 immunoglobulin variable gene mutation (or its surrogate Zap 70) 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.

Beta-2-microglobulin may have prognostic significance though whether or not this adds to the other factors is uncertain. Computed tomography (CT) scans is useful to follow and monitor disease progression when adenopathy or is present. For anemic patients, reticulocyte counts and a direct Coombs' test should be performed to evaluate for the possibility of hemolysis.

The National Cancer Institute sponsored working group (NCI-WG) first published the guidelines for the diagnosis and treatment of CLL in 1996.[32] The recent developments in the use of prognostic markers and treatment options for CLL have led to the revision of these guidelines, particularly the response criteria.[33] Complete and partial responses are considered clinically beneficial. Relapse is defined as the disease progression after a period of 12 months or more following complete or partial responses. Refractory disease is defined as the one which does

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respond to purine analog-based therapy or which progresses within 12 months after receiving such therapy.

Treatment

Locoregional radiation therapy (RT) is an appropriate induction therapy for patients with localized SLL (Ann Arbor stage I). In rare patients, radiation may be contraindicated or it may be a sub-optimal therapy due to the presence of comorbidities or the potential of long-term toxicity. Patients with localized SLL that has progressed after initial RT and those with advanced CLL or SLL (Ann Arbor stage II-IV) are treated with chemoimmunotherapy or chemotherapy. Chemotherapy regimens that have shown efficacy in clinical trials include chlorambucil or cyclophosphamide given with or without prednisone, purine analog-based regimens, or an alkylating agent-based combination chemotherapy regimen such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone).

In the CALGB 9011 study, 509 patients were randomized to receive fludarabine, chlorambucil or the combination.[34] The combination arm was stopped due to excessive toxicity. Complete remission (20% vs. 4% for chlorambucil), partial remission (43% vs. 33% for chlorambucil), median duration of remission and median PFS were significantly better in patients treated with fludarabine. The study found no significant difference in OS between the two arms suggesting that in some circumstances, chlorambucil as initial therapy may be appropriate. A 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.[35] Fludarabine and CHOP produced similar overall remission rates (71%) compared to CAP (58%). However, fludarabine was better tolerated than CHOP.

In large randomized trials (US Intergroup E2997 and UK Leukemia Research Fund CLL 4), the combination of fludarabine and cyclophosphamide was associated with an increase in overall response, CR and PFS compared to fludarabine alone.[36,37] E2297 trial also reported that IgV_H, CD38 or ZAP-70 expression did not predict outcome of fludarabine-based therapy.[38]

Rituximab is a monoclonal antibody against CD 20, which has been approved by FDA for the treatment of indolent lymphoma. Rituximab has been evaluated in combination with fludarabine-based chemotherapy. CALGB study 9712 compared the efficacy of fludarabine with concurrent or sequential administration of rituximab in untreated patients with CLL.[39] The concurrent regimen was associated with a higher overall response rate (90% vs. 77% for the sequential regimen) at the expense of higher grade 3 or 4 toxicity. However, comparison of the outcomes of patients treated with fludarabine alone in the CALGB 9011 trial and the pooled results from the CALGB 9712 study, suggested that the addition of rituximab to fludarabine prolongs PFS and OS.[40] The combination of fludarabine, cyclophosphamide and rituximab (FCR) has been evaluated at MD Anderson Cancer Center both as initial therapy for progressive or advanced CLL and as second-line therapy for relapsed or refractory CLL. [41,42] FCR regimen produced high overall response rate and CR.

The combination of pentostatin and cyclophosphamide (PC) with or without rituximab (R) has shown significant activity in previously treated patients with relapsed or refractory disease.[43,44] In a small number of previously treated patients, the response rates were similar for PC and PCR. However, based on a historical retrospective comparison with PC regimen, the median duration of response for PCR (25 months) is longer than that of PC (7 months) as well as median survival (44 months for PCR and 16 months for PC). The addition of rituximab

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showed a survival advantage. Based on these results, the CLL Research Consortium members initiated a trial of PCR in previously in untreated patients.[45] Responses were observed in 91% of patients (41% CR, 21% nodular PR and 28% PR).

Alemtuzumab is a monoclonal antibody targeting CD 52. In a large international study, alemtuzumab induced significant responses in patients who had failed fludarabine-based therapy. Median time to progression was 4.7 months and median OS was 16 months (32 months for responders).[46] Alemtuzumab has also been effective in patients with fludarabine refractory CLL and del(17p) or p53 gene mutations.[47,48] In an international, multicenter randomized study (CAM307), PFS and overall response rate (83% vs. 55%) were significantly better for alemtuzumab compared to chlorambucil, as first-line treatment for patients with CLL.[49] However, nodal sites of disease have generally not responded well with single agent alemtuzumab.

In patients with localized SLL (Ann Arbor stage I) that has progressed after initial RT or those with advanced disease (Ann Arbor stage II-IV disease) with no del (17p), treatment options depend on the presence or absence of the following indications: symptoms, threatened end-organ function, cytopenia, bulky disease, steady progression, histologic transformation, recurrent infections and/or patient's preference. Patients with no indications for treatment can be observed until disease progression. Those presenting with any of the above indications should be treated with chemotherapy (single agent or combination) or chemoimmunotherapy regimens suggested in CSLL-D. Purine analog-based therapy is preferred. Prophylaxis for tumor lysis syndrome (TLS) should be considered since patients with CLL are at risk of developing TLS.

NCCN guidelines suggest the following regimens (which by convention are listed in alphabetical order) for first-line therapy, with or without rituximab: Chlorambucil with or without prednisone; cyclophosphamide with or without vincristine and/or prednisone; CHOP regimen for patients who are unable to tolerate fludarabine; fludarabine (F) alone or in combination with cyclophosphamide (FC) and PCR regimen (pentostatin, cyclophosphamide and rituximab).

Bendamustine is an alkylating agent with a low cross-resistance with other alkylating agents (chlorambucil, cyclophosphamide, ifosfamide) and fludarabine. In a pivotal phase III study, bendamustine was compared to chlorambucil in patients with untreated CLL.[50] At a median follow-up of 18.5 months, bendamustine produced an overall response rate (ORR) of 68% with a CR of 30%, which was significantly higher than that of chlorambucil (39% with CR of 2%). Median progression-free survival (21.7 months vs. 9.3 months for chlorambucil) and median duration of remission (18.9 months vs. 6.1 months with chlorambucil) were also better for bendamustine. However, there were no differences in OS between the two groups.

Based on the results of this study, FDA recently approved bendamustine for the treatment of patients with CLL. However, the efficacy of bendamustine compared to other first-line therapies for CLL other than chlorambucil has not yet been established. NCCN guidelines have included bendamustine as a single agent for first-line therapy; single agent or in combination with rituximab for second-line therapy.

Patients who achieve a complete or PR following induction therapy are generally observed. Additional therapy for patients in remission is investigational and should be given only in the context of a clinical trial. Treatment options for patients with disease progression are similar to those available as initial therapy. Allogeneic stem cell rescue is an

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alternate treatment option for patients with relapsed disease but would generally be used after re-induction of remission.[51] The choice of second-line therapy should take into account the remission duration as well as the initial agents used. Any of the chemotherapy regimens recommended for first-line therapy can be used for progressive disease, in combination with either rituximab or alemtuzumab. The panel has also included alemtuzumab as a single agent for second-line therapy in all patients with relapsed or refractory CLL.

Presence of del(17p) is associated with a poor response to conventional therapy; treatment options for patients with del(17p) depend on their age. Alemtuzumab is a treatment option for patients 70 years or older. Those younger than 70 years are treated with chemotherapy or chemoimmunotherapy regimens suggested in CSLL-D. Patients with CR are usually observed. High dose therapy with allogeneic stem cell rescue is a treatment option for those who achieve CR or PR. Patients who are not responsive to chemotherapy are treated with alemtuzumab. High dose therapy with allogeneic stem cell rescue can be considered for patients showing response.

Patients with autoimmune cytopenia may require therapy targeted to the hemolysis. Initial therapy for autoimmune hemolytic anemia (AIHA) and immune thrombocytopenic purpura (ITP) is administration of corticosteroids. Intravenous immunoglobulin may be used in the treatment of refractory disease. Patients with AIHA should be observed carefully during treatment and the presence of AIHA should not absolutely preclude the use of fludarabine-based therapy. Rituximab or splenectomy are options in select patients. Immunosuppressive agents such as prednisone, cyclosporine, and antithymocyte globulin (ATG) are indicated for the treatment of pure red cell aplasia. Patients with recurrent infections, particularly those patients with encapsulated organisms in the setting of hypogammaglobulinemia, may benefit from intravenous gamma globulin.

Cytomegalovirus (CMV) reactivation is well documented in patients receiving alemtuzumab.[52] Due to the high risk of CMV reactivation, CMV viremia should be measured by PCR quantization at least every 2-3 weeks. The current management is controversial. Ganciclovir is used either prophylactically if viremia present, or in some cases only if viral load is rising.

Follicular Lymphoma

Diagnosis

Follicular lymphoma has a characteristic immunophenotype, which includes CD20+, CD10+, bcl-2+, CD23+/-, CD43-, CD5-, and cyclin D1-. Rare cases of FL may be CD10- or bcl-2-. Additional paraffin-embedded material is useful, under certain circumstances, for immunophenotyping to evaluate the expression of bcl-6, cyclin D1 (if CD10- and/or CD5+ or CD43+), CD43, kappa/lambda, CD21, and Ki-67. Ninety percent of cases have a chromosome translocation, t(14;18), which juxtaposes the bcl-2 gene with the immunoglobulin heavy-chain locus that results in the deregulated expression of bcl-2. The diagnosis is easily established on histological grounds, but immunophenotyping is encouraged to distinguish from a nodular MCL or SLL. Molecular genetic analysis to detect bcl-2 rearrangement, cytogenetics or FISH to identify t(14;18) will be useful under certain circumstances.

In the REAL/WHO classification FL is classified into three histological grades according to the number of centroblasts utilizing the counting method of Mann and Berard (Grade 1: 0-5 centroblasts per high power field (HPF); Grade 2: 6-15 centroblasts per HPF and Grade 3: greater

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than 15 centroblasts per HPF). NCCN guidelines apply to FL (grades 1-2). FL (grade 3) is commonly treated according to DLBCL.

Workup

The diagnostic workup for FL is similar to the workup for other indolent lymphomas. The majority of patients 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 to document clinical stage I-II disease. This can be deferred if observation is the initial treatment option. The FLIPI (Follicular Lymphoma International Prognostic Index) may be used in determining treatment prognosis but has not been established as a means of selecting treatment options.[53] FLIPI includes patient characteristics (age), tumor burden which is determined by Ann Arbor stage and number nodal sites involved, hemoglobin levels and tumor aggressiveness as determined by serum LDH levels. The majority of NCCN investigators 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.[54]

Treatment

The therapeutic approach to follicular lymphomas (grades 1 and 2, WHO classification) depends on the extent of initial disease involvement. Follicular lymphomas, grade 3 (WHO/REAL classification) are generally treated according to the guidelines for DLBCL, though they are recognized to have a much higher risk of relapse. It should be noted that in most centers the proportion of patients diagnosed with FL, grade 3 is greater than that previously diagnosed as follicular large cell lymphoma in the International Working Formulation.

In a prospective randomized study conducted by M.D. Anderson Cancer Center, the addition of adjuvant CHOP to RT did not improve relapse free survival in patients with low-grade lymphoma.[55] Locoregional RT (24-30 Gy, with an additional 600 cGy in selected patients with bulky or slowly regressing disease) is the preferred treatment option for patients with non-bulky localized (Ann Arbor stage I-II) disease. The NCCN guidelines have included immunotherapy with or without chemotherapy or RT as an alternate treatment option with a category 2B recommendation. In circumstances where toxicity of IFRT outweighs the potential clinical benefit, observation may be appropriate. If there is no response to initial therapy, patients should be managed in the same manner as patients with systemic presentation of FL, as described below.

Patients who present with bulky abdominal (Ann Arbor stage II) or stage III-IV disease, the decision to treat is based on the following indications: symptoms, threatened end-organ function, cytopenia secondary to lymphoma, bulky disease, steady progression, and/or patient preference. The selection of treatment should be highly individualized according to age, extent of disease, 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 high-dose therapy with autologous stem cell support. Since FL is currently incurable with conventional therapy participation in a clinical trial should be considered for first-line treatment. In the absence of an appropriate clinical trial, patients with indications for treatment should be treated with systemic therapy. In selected cases, IFRT may be used for local palliation. Asymptomatic patients can be observed.[56]

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Single agent cyclophosphamide had equivalent OS and CR rates compared to cyclophosphamide-based combination chemotherapy.[57] Rituximab produced an overall response rate of 67% in chemotherapy-naïve patients compared to 46% in pretreated patients with FL. Prolonged administration of rituximab (one dose every 8 weeks four times) significantly improved event-free survival in chemotherapy-naïve patients but did not extend OS.[58] However, retreatment with rituximab at progression provided the same duration of benefit as did maintenance (4 weekly doses every six months for two years) with fewer doses of rituximab.[59] NCCN guidelines recommend rituximab (preferred), or alkylating agents such as cyclophosphamide or chlorambucil as single agents for first-line therapy in elderly or infirm patients.

Chemoimmunotherapy is another option for first-line therapy in patients with advanced disease. The addition of rituximab to combination chemotherapy regimens has consistently increased the overall response rate, response duration and PFS. In addition, some studies have demonstrated OS benefit; a recent meta-analysis has confirmed the benefit in OS despite what is still limited follow up for FL.[60]

The safety and efficacy of R-CHOP was demonstrated in a small study that demonstrated excellent long-term results.[61,62] The superiority of R-CHOP to CHOP in treatment naïve patients was established in a prospective randomized phase III study conducted by the German Low-Grade Lymphoma Study Group (GLSG) involving 428 patients. R-CHOP was associated with a 60% reduction in the relative risk for treatment failure, significantly prolonged time to treatment failure, higher overall response rate and prolonged duration of remission.[63] Overall survival analysis is complicated by a second randomization which included HDT/ASCR. There OS was the same with and without rituximab, if there was consolidation with HDT/ASCR. However, OS was significantly improved for patients receiving R-CHOP followed by interferon compared to CHOP followed by interferon. R-CHOP also improved outcome of elderly patients with previously untreated FL.[64] In the ECOG 1496 trial, addition of rituximab to CVP (cyclophosphamide, vincristine and prednisone) chemotherapy significantly improved outcome in patients with previously untreated FL, with no significant increase in toxicity.[65] At a median follow-up of 30 months, prolonged time to progression was 32 months for patients treated with R-CVP versus 15 months for those treated with CVP.[65]

The addition of rituximab to fludarabine or fludarabine-based combination has improved outcomes in various clinical studies.[66-69] In a prospective randomized trial, FCM-R regimen (fludarabine, cyclophosphamide, mitoxantrone and rituximab) was associated with superior outcomes in patients with relapsed or refractory FL and MCL.[67] In another randomized trial, concurrent administration of rituximab with FND regimen (fludarabine, mitoxantrone and dexamethasone) resulted in a significantly higher 3-year failure-free survival rate (84% vs. 59% for sequential arm) in a subset of patients with FL.[68]

Radioimmunotherapy (RIT) with [^{131}I]-tositumumab and ^{90}Y-ibritumomab tiuxetan is an alternate treatment option for relapsed, refractory or histologically transformed FL.[70-73] Recent reports from clinical trials using [^{131}I]-tositumumab or [^{90}Y]-ibritumomab tiuxetan as first-line treatment, either alone or following chemotherapy, have demonstrated high response rates and PFS.[74-77] Initial treatment with single one-week course of ^{131}I-tositumomab induced prolonged clinical and molecular remissions in patients with advanced FL.[74,75] In the Southwest oncology Group (S9911) trial, CHOP followed by RIT with [^{131}I]-tositumomab resulted in an overall response rate of 91%, including a 69% complete remission (CR) rate in patients with previously untreated FL.[76] After a median follow-up of 5 years, the estimated

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5-year OS rate was 87%, and PFS rate was 67%. In historical comparison, these statistics were better than those reported for CHOP alone. In a recent phase II study, R-CHOP (3 cycles) followed by ^{90}Y-ibritumomab tiuxetan induced high CR in patients with previously untreated FL.[77] In another recent randomized trial (FIT) of induction chemotherapy with or without adjuvant RIT showed a highly significant improvement in CR rate and prolongation of PFS.[78]

Suggested treatment options for patients with advanced FL are listed in FOLL-B. Based on the reported data, rituximab in combination with CHOP or CVP chemotherapy for first-line therapy in patients with advanced FL now has a category 1 recommendation. Other suggested regimens include rituximab either as a single agent or in combination with fludarabine-based chemotherapy. RIT either alone or following treatment with CHOP with rituximab is included as category 2B option for first-line treatment. CHOP plus rituximab followed by RIT is recommended only in the context of a prospective clinical study.

Bendamustine (recently approved for the treatment of CLL) has also been investigated as a single agent or in combination with other chemotherapeutic agents in low grade NHL.[79,80,81,82] In a recent report from a phase II multicenter study, bendamustine as a single agent showed promising results with acceptable toxicity in heavily pretreated patients with rituximab-refractory indolent or transformed NHL.[82] An ORR of 77% (15% CR, 19% unconfirmed CR and 43% PR) was observed. Among patients with FL, 82% ORR was observed. At a median follow-up of 26 months, median PFS was 7.1 months for all patients. In another study conducted by German study group, the patient population included both relapsed low grade NHL and MCL.[79] Bendamustine in combination with rituximab produced an ORR of 96% (71% CR and 25% PR) in a subset of patients with relapsed or refractory FL. Median duration of follow-up was 20 months.

At ASH 2007, Rummel et al. presented the results of a randomized comparison of bendamustine and rituximab (BR) with R-CHOP as first-line therapy for patients with indolent lymphoma and MCL.[83] The trial, StiL (Study Group Indolent Lymphomas) NHL 1-2003, was designed as an equivalency study and the first interim analysis of 315 evaluable patients suggested that the response rates and response durations are the same for BR and R-CHOP. Furthermore, BR was associated with less toxicity compared to R-CHOP. However, the NCCN panel felt that these data were preliminary and further follow up of the entire patient population was necessary prior to recommending BR as first-line therapy. In ongoing phase III clinical studies, the combination of bendamustine and rituximab is being compared with fludarabine and rituximab in relapsed low grade NHL.

The panel has included bendamustine with or without rituximab as an option for second-line therapy for patients with relapsed or refractory FL, based on the data available in the literature. However, this is only a category 2B recommendation since no data is available yet from randomized control studies evaluating bendamustine versus other conventional chemotherapy regimens used for the management of low grade NHL and there was not uniform consensus among the panel.

Rituximab should be used with caution in hepatitis-B patients. IFRT with or without systemic therapy can be considered for palliation in patients with locally bulky or symptomatic disease. In patients who may be eligible, at a later time, for high dose therapy followed by autologous stem cell rescue (HDT/ASCR), profoundly myelotoxic regimens should be avoided.

Follow-up of patients with a CR or PR includes repeat diagnostic tests, as indicated, such as imaging tests based on the site of disease and clinical presentation. At recurrence, biopsy is generally indicated to

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exclude histologic transformations, especially if there are raising LDH levels, disproportional growth in one area, development of extranodal disease or new "B" symptoms.

Transformation to DLBCL is common in patients with FL occurring at a rate of approximately 2-3% per year for at least 15 years and the risk of transformation falls after that time, for reasons that remain unclear. [84] Non-uniform uptake on a FDG-PET scan can be an indication of transformation; areas of high SUV, especially in excess of 13.1 are suspicious for transformation. Transformation to DLBCL is generally associated with a poor clinical outcome; however, in cases where it occurs and the patient has had minimal or no prior chemotherapy, anthracycline-based therapy with or without RT or chemotherapy with or without rituximab are treatment options with good outcomes. [85] If the patient has had multiple prior therapies, the prognosis is much poorer; RIT or IFRT are treatment options. Autologous or allogeneic stem cell rescue can be considered in patients with responsive disease after initial treatment.

In the setting of relapsed/refractory disease, rituximab maintenance following first line therapy has been shown in two large-scale randomized trials to provide a PFS advantage over observation for patients treated with chemoimmunotherapy.[86,87,88] In a phase III Intergroup trial (EORTC 20981), maintenance rituximab considerably improved PFS (51.5 months vs. 14.9 months for observation) and OS (85% at 3 years versus 77% with observation) in patients with relapsed or resistant FL responding to CHOP or R-CHOP. [87] The improvement in PFS was seen in a subset analysis of the patients having received R-CHOP. In another prospective randomized study by the GLSG, rituximab maintenance after second line treatment with R-FCM (rituximab with fludarabine, cyclophosphamide and mitoxantrone) significantly prolonged duration of response in patients with recurring/refractory FL or MCL.[88]

Treatment for relapsed or progressive disease is based on the presence or absence of indications for treatment. Patients with indications for treatment can be treated with chemoimmunotherapy as described above for first-line treatment, RIT or any of the second-line regimens used for patients with DLBCL. Rituximab maintenance following initial therapy has demonstrated benefit in PFS for patients with relapsed or refractory disease but its role in improving outcome of patients in first remission remains investigational. The PRIMA trial evaluating the role of rituximab maintenance following chemoimmunotherapy has completed accrual and preliminary results are anticipated late 2008. This trial should help clarify the role of rituximab maintenance as an adjuvant to initial remission induction. In the NCCN guidelines, its use in this situation is a category 2B recommendation.

HDT/ASCR is an appropriate option for patients with refractory, relapsing or progressive disease, if a subsequent remission can be induced; though HDT/ASCR is generally not curative, the benefit can be durable with median PFS of 3-5 years.[89,90] In selected patients, ablative and nonmyeloablative allogeneic stem cell rescue have shown long term survival benefit although there is a treatment related mortality rate of 10-25% for non-myeloablative and 40% for myeloablative.

Marginal Zone Lymphomas

Marginal zone lymphomas (MZL) are a heterogeneous group of disorders consisting of extranodal marginal zone lymphoma (MALT lymphoma), nodal MZL, and splenic MZL. MALT lymphomas are subdivided into the gastric and non-gastric lymphomas. Splenic MZL

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involves the spleen and bone marrow, whereas nodal MZL occurs primarily in the lymph nodes though additional extra nodal sites are common.

Adequate hematopathology and immunophenotyping are needed to establish a diagnosis. The typical immunophenotype of MZL is CD5-, CD10-, CD20+, CD23-/+, CD43-/+, cyclin D1-, bcl-2 follicles-. In addition splenic marginal zone lymphoma is characterized by annexin-1- and CD103-. Immunophenotyping is useful in distinguishing MZLs from CLL (CD5+) and MCL (CD5+) and hairy cell leukemia (annexin-1+ and CD103+). Molecular, cytogenetics or FISH evaluation for the t(11;18) chromosomal translocation, is recommended. The t(11:18) is the most common genetic abnormality found in patients with gastric MALT lymphomas. It is associated with disseminated disease and resistance to antibiotic treatment in patients with gastric MALT lymphoma.[91,92] In some cases cytogenetic evaluation should include evaluation for t(3;14)(p14.1;q32) [IGH-FOXP1]; t(1;14)(p22;q32) [IgH-BCL10]; t(14;18)(q32;q21) [IGH-MALT1] and del (7q31-32).

Gastric MALT Lymphoma

Gastric MALT lymphomas develop in the stomach. *Helicobacter pylori* (*H. pylori*) infection has a critical role in the pathogenesis of this disease and its eradication can lead to tumor remission.[93] Other MZLs have been shown to be associated with infectious agents, but this association has not been validated.[94,95,96]

Workup

The workup for gastric MALT lymphoma is similar to the workup for other NHLs. Special aspects of the workup for gastric MALT lymphoma include direct endoscopic assessment of the gastrointestinal tract and additional evaluation of the tumor specimen for the presence of *H.pylori.* The presence pf H.pylori infection must be confirmed by biopsy with PCR (polymerase chain reaction) and urea breath test. Nondiagnostic atypical lymphoid infiltrates that are *H.pylori* positive should be re-biopsied to confirm or exclude lymphoma prior to treatment of *H.pylori*. Appropriate imaging studies include CT of the chest, abdomen and pelvis, and in select cases, bone marrow biopsy. 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 that is essential information in some of the currently used staging systems.

Staging

Several different staging systems have been for gastric MALT lymphomas. In the Lugano staging system, Ann Arbor stage III has been removed and supradiaphragmatic nodal disease is included under stage IV. TNM (Tumor-Node-Metastasis) 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. In contrast, cases with disseminated nodal involvement appear to behave more like nodal MZL or like disseminated FL.

Treatment

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 numerous trials.[97,98,99] Approximately two thirds of patients with localized gastric MALT lymphoma have a complete tumor remission after eradication of *H.pylori* infection with antibiotic therapy.[100] However, there is increasing evidence that late relapses occur after

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antibiotic management and a long duration of follow-up is appropriate.[101]

For disease confined to the stomach (stage IE, H.pylori positive), treatment begins with antibiotics in combination with a proton pump inhibitor to block gastric acid secretion. The tumor response may be slow, and re-evaluation with endoscopy should not be done until 3 months post treatment unless clinical deterioration is evident. If there is evidence of the t(11;18) t(1;14), t(14;18)(q32;q21), treatment of the *H.pylori* infection with antibiotics may be ineffective and these patients should be considered for alternative therapy. H. Pylori infection is not evident in approximately 10-40% of patients with gastric MALT lymphomas.[102] IFRT is preferred for patients with disease that is extending to the muscularis or disease extending from the GI tract to adjacent organs (stages IE [T2 or T3] or IIE H.pylori negative), particularly if one of the t(11;18), t(1;10), or t(14;18)(q32;q21) translocations is present.[103] Rituximab or chemoimmunotherapy are other treatment options.[104]

In patients with disseminated disease (stage III or IV), treatment is similar to that described for other advanced-stage indolent lymphomas. As with other indolent lymphoma, 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 bleeding, early satiety), bulky disease at presentation, steady progression of disease, or patient preference. Treatment may include single-agent or combination chemotherapy, or locoregional RT. If there is evidence of recurrence, patients are managed according to the FL guidelines. Surgical resection is generally limited to specific clinical situations. Though disease control is excellent with total gastrectomy, the long-term morbidity has precluded routine surgical resection. Total gastrectomy is necessary because of the multi-focal nature of the disease.

Follow-Up Endoscopy

Following primary antibiotic therapy, patients are restaged with endoscopy and biopsy after 3-months. Patients with responsive disease (microbiologic and tumor response) are just observed. Patients with persistent lymphoma with no evidence of *H.pylori* are treated with RT, if they are symptomatic or if there is significant disease progression. Asymptomatic patients can be observed for 3 months. Locoregional RT can be considered as early as 3 months after observation but observation can be prolonged for up to 18 months (category 2B). Patients with persistent *H.pylori* and regressing or stable lymphoma are treated with second-line antibiotics. Lastly, patients who are *H.pylori* positive with persistent lymphoma are treated with RT, if they have progressive disease. Those with stable disease are treated with second-line antibiotics.

Follow-up surveillance at 6 months consists of repeat endoscopy and biopsy. Patients can be subdivided into the same four groups, as above. Patients with complete tumor response continue to be observed if the *H. pylori* is negative, or they can be treated with other antibiotic therapy if *H. pylori* remains positive. Patients with persistent or recurrent lymphoma after antibiotic therapy, irrespective of their H.Pylori status, are treated with locoregional RT if not previously treated. Patients whose disease does not respond to radiation are managed with single-agent or combination chemotherapy similar to FL. Following second-line antibiotic therapy or RT, patients are again evaluated with endoscopy and biopsy to rule out large cell lymphoma. Systemic therapy as indicated in FOLL-3 is recommended for recurrence following CR to RT or antibiotic therapy, or for patients with no response to prior RT.

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Non-gastric MALT Lymphomas

Nongastric MALT lymphomas can arise from a large number of non-gastric sites such as lung, thyroid, salivary glands, breast, and tissues surrounding the eye. For patients with stage IE -II disease or extranodal disease involving multiple sites, locoregional RT (20-30 Gy) is appropriate. Surgery may be considered for certain sites of disease (eg, lung, skin, thyroid, colon, small intestine, and breast). If there is no residual disease following surgery, patients are observed, whereas those with positive surgical margins are treated with locoregional RT. Recurrence following primary treatment is managed similar to advanced stage FL. RT is an option for those with local recurrence. Patients with advanced-stage disease (stage III-IV) are managed the same as patients with FL. Aggressive histologies, in which MALT lymphomas coexist with large cell lymphoma, should be managed according to the diffuse large B-cell practice guidelines.

Nodal Marginal Zone Lymphoma

Nodal MZL is rare and often presents concurrently with extranodal sites of disease. The diagnosis of nodal MZL requires careful evaluation to rule out extranodal sites of disease and it must be distinguished from nodal FL, MCL, lymphoplasmacytic lymphoma and CLL, all of which are more common. Nodal MZL is managed as per FL.

Splenic Marginal Zone Lymphoma

Diagnosis

Splenic MZL is often presumptive based on the findings of splenomegaly with peripheral blood flow cytometry usually revealing a monoclonal B cell population.[105] Involvement of the bone marrow is also common. This lymphoma is distinguished from CLL by the absence of CD5 expression, strong CD20 expression and variable CD23 expression. In some cases, the diagnosis can be established by the finding of villous projections on the circulating lymphocytes. Splenectomy can definitively establish the diagnosis and in many cases is therapeutic as well.

Workup

The workup is similar to the other indolent lymphomas. Flow cytometry of peripheral blood and bone marrow is essential in identification of a monoclonal B cell population. CT of the chest, abdomen, and pelvis will help in establishing the extent of disease. 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.[106]

Treatment

Most of the patients with no splenomegaly, cytopenia or other symptoms can be observed. Patients presenting with splenomegaly are treated depending on their hepatitis C status. Hepatology evaluation is recommended for hepatitis C positive patients; anecdotal tumor regressions have been reported in responses to hepatitis therapy. In all other patients, in the absence of cytopenias or other symptoms, patients should be observed.

In a retrospective study, rituximab-based treatments resulted in longer failure free survival in patients with splenic MZL compared to patients treated with chemotherapy alone.[107] Rituximab was superior to splenectomy in normalizing white blood cell and absolute lymphocyte counts. Splenomegaly also disappeared in 92% of the patients treated with rituximab alone.

Splenectomy is the preferred option for patients with cytopenias or symptoms of weight loss, early satiety or abdominal pain. Rituximab is

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another treatment option for this group of patients. Patients should be monitored on a regular basis. If there is disease progression, patients are managed similar to advanced stage FL.

Mantle Cell Lymphoma

Diagnosis

Mantle cell lymphoma can be readily distinguished from other small lymphocytic lymphomas due to the widespread availability of appropriated diagnostic reagents.[108] The diagnosis can be established by histological examination in combination with immunohistochemistry with a profile consisting of CD5+, CD10-/+, CD20+, CD23-, CD43+, and cyclin D1+. Rare cases of MCL may include CD5- or CD 23+ immunophenotype. The diagnosis of MCL requires the expression of cyclin D1, an opinion shared by the panel.[109] However, recent gene profiling data suggests that cyclin D1 expression may not be required for the molecular signature of MCL; in these cases, over-expression of cyclin D2 or D3 can be observed. [110] Cases with a typical immunophenotype, CD5+, CD23-, CD20+ that are cyclin D1- should be evaluated for cyclin D2 and D3 expression; positive cases should be classified as MCL with a variant immunophenotype, negative cases should be classified as variant SLL/CLL. Currently available reagent for immunohistochemistry of cyclin D1 are robust and yield good staining; however, in some cases cytogenetics or FISH for the t(11;14), juxtaposing the cyclin D1 locus with the IgH locus can be diagnostically helpful.[111]

Workup

The workup for MCL is similar to the workup for many indolent lymphomas and certain aggressive lymphomas. MCL is a systemic disease with frequent involvement of the bone marrow, gastrointestinal tract and frequently a leukemic phase. For this reason, both the peripheral blood and bone marrow must be carefully evaluated for the presence of malignant cells. Chest, abdominal, and pelvic CT scans are routinely performed. MCL may present as lymphomatous polyposis coli and colon involvement is common.[112] In the current guideline, colonoscopy is now considered a routine part of the evaluation of MCL. Post treatment colonoscopy is necessary to confirm a CR, if it was not done previously. Upper endoscopy and neck CT scan may be helpful in selected cases. In patients with the blastic variant, lumbar puncture is done to evaluate the spinal fluid for involvement.

Treatment

It has generally been thought that MCL has the worst characteristics of both indolent and aggressive non-Hodgkin's lymphomas owing to the incurability with conventional chemotherapy and it more aggressive growth pattern. However, emerging data suggests that the long-term outcome of patient with MCL may be improving.[113] There remains no established standard of care. In the absence of standard management for MCL, patients with this disease should be referred for participation in prospective clinical trials. Like the management of patients with indolent lymphoma patients with MCL often have highly individualized course of care.

Several regimens have shown significant activity in newly diagnosed MCL, but none of these regimens are curative in patients with advanced disease.[114,115] Recent metal analysis has shown that the addition of rituximab to chemotherapy increases response rates but it has not yet been proven to extend either progression-free or OS.[60] R-CHOP was significantly superior to CHOP in terms of overall response rate (94% v 75%), complete remission rate (34% v 7%).[116,117] No differences were observed for PFS. In patients with newly

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diagnosed MCL, R-HyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with R-MA (rituximab plus high-dose methotrexate and cytarabine) produced a 3-year failure-free survival (FFS) rate of 64% and OS rate of 82%.[118] However, in a subset of patients more than 65 years of age, this regimen was associated with shorter FFS and significant toxicity. R-HyperCVAD was evaluated in a multicenter SWOG study that reported a CR/CRu rate of 58% and 2-year PFS of only 63%. [119] Modified R-HyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone) regimen developed by the Wisconsin Oncology Network, produced favorable overall response rate (77%) and CR rate (64%) with acceptable toxicity in patients with untreated MCL.[120] This is being tested more widely in an ongoing ECOG trial. RIT has also been investigated as initial therapy as well as second-line treatment for refractory or relapsed MCL as reviewed by Zelenetz.[115]

Few patients present with localized MCL and the available published literature on management is retrospective and anecdotal.. In a retrospective analysis of 26 patients with early stage MCL, inclusion of RT was associated with an improved PFS and a trend towards improved OS.[121] Outside of a clinical trial, the panel recommended IFRT with or without combination chemotherapy. These recommendations are based on treatment principles in the absence of more definitive data.

Majority of patients with MCL will have advanced stage disease and require systemic therapy. Highly selected patients who are asymptomatic with stable adenopathy and non-bulky disease are observed; these patients usually have low bulk, nodular morphology variant and a low proliferation fraction. Based on the available data, the panel has included R-HyperCVAD and R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin)[122] as options for first-line therapy. In patients older than 65 years of age, the panel recommends the use of modified HyperCVAD regimen with rituximab maintenance. CHOP (with or without rituximab) is recommended for selected older patients who cannot tolerate intensive therapy.

Initial remission should be followed by HDT/ASCR in eligible patients, as this has been associated with some evidence of durable remission. In a study conducted by M.D. Anderson Cancer Center, ASCR following treatment with hyperCVAD regimen for cytoreduction prolonged OS in patients with MCL in first disease remission, especially in those with a low beta-2-microglobulin level.[123] In a randomized trial conducted by European MCL network, patients 65 years of age or younger with advanced-stage MCL were randomized to ASCR or maintenance with interferon-alpha after achieving of complete or partial remission by CHOP-like chemotherapy. Three-year OS was 83% after ASCR versus 77% in the IFN group.[124]

The optimal approach to recurrent disease remains to be defined. Fludarabine-based combination regimens such as fludarabine in combination with cyclophosphamide[125] and FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab) have shown activity in MCL. In a prospective randomized study of the GLSG, addition of rituximab to the combination of fludarabine, cyclophosphamide, mitoxantrone, produced significantly longer OS in patients with relapsed and refractory MCL.[66] Cladribine also has shown activity in patients with untreated or relapsed MCL, achieving a response rate of 58%.[126] In a phase II trial, the proteosome inhibitor bortezomib induced 33% response rate including 8% CR in patients with relapsed or refractory MCL.[127] Median time to progression was 6.2 months. Based in these data, bortezomib received FDA approval for the treatment of patients

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with MCL who have received at least one prior therapy. Studies of bortezomib-based combinations in MCL are ongoing. Marked anti-tumor activity has been shown for rituximab plus thalidomide in patients with relapsed or refractory MCL.[128] Lenalidomide, an immunomodulator related to thalidomide also has activity in MCL either alone or in combination with rituximab.

Bendamustine is an emerging agent (recently approved for the treatment of CLL) that has well-documented activity in patients with MCL.[79,80,81] In a phase II study conducted by the German study group (which included low grade NHL and MCL patients), the subset of patients with relapsed or refractory MCL treated with the combination of bendamustine and rituximab has an overall response rate of 75% with a CR rate of 50%.[79] Median follow-up duration was 20 months. The median PFS for MCL patients was 18 months whereas the median PFS for patients with FL had not been reached. Further studies are needed to confirm these findings.

Based on the efficacy data available in the literature, the combination of bendamustine with or without rituximab is included in the guidelines as an option for second-line therapy for patients with relapsed or refractory MCL, with a category 2B recommendation since no data is available yet from randomized studies and there was not uniform consensus among the panel. Ongoing phase III studies are evaluating the efficacy of bendamustine plus rituximab vs. R-CHOP in previously untreated MCL patients.[83] The panel felt that additional follow-up from this study was necessary prior to making recommendations regarding initial therapy. The same combination is also being compared to fludarabine with rituximab in relapsed MCL.

Patients with relapsed disease following CR to induction therapy, those who obtain only a PR to induction therapy or those with progressive disease are appropriate candidates for clinical trials of high-dose therapy with stem cell rescue. Alternatively, these patients can also be treated with second-line chemotherapy or HDT/ASCR.[129] Suggested regimens for second-line therapy for relapsed or refractory disease are listed in MANT-A.

Diffuse Large B-Cell Lymphoma

Diagnosis

Diffuse large B-cell lymphomas are the most common lymphoid neoplasms in adults. FL (grade 3), DLBCL coexistent with FL of any grade, gastric MALT or non-gastric MALT lymphoma are also managed according to the DLBCL guidelines.

Recent studies with gene expression microarray analysis of DLBCL have revealed significant heterogeneity within this diagnosis.[130,131] However, incorporation of this information into treatment algorithms awaits further investigation. The immunophenotypic studies used to distinguish DLBCL from other lymphoid entities include T-cell markers (peripheral T-cell lymphoma), CD30 (anaplastic large cell lymphoma), and TdT and CD79a (lymphoblastic lymphoma). The typical immunophenotype is CD20+, CD45+, and CD3-.

Immunohistochemical markers CD10, BCL6, and MUM1 have been reported to recapitulate the gene expression profiling separating patients into tumors derived from germinal center (GC) origin (CD10+, or BCL6+, MUM1-) and non-GC orgin (CD10-, MUM1+ or BCL6-, MUM1-).[132] However, the validity of this classification scheme has been brought into question; further, work needs to be done to identify a robust IHC for GC vs. non-GC.

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Workup

The staging workup is designed to identify all sites of known disease and determine prognosis with known clinical risk factors. Risk factors used by the IPI include age, stage of disease, serum lactate dehydrogenase (LDH) level, performance status, and the number of extra-nodal sites of disease. In patients who are 60 years or younger, the prognostic factors include tumor stage, performance status, and serum LDH level. The International Prognostic Index (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. [133]

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. PET scans have now been incorporated into the response criteria. In some centers, beta-2-microglobulin is considered a major determinant of risk (category 2B). Lumbar puncture is indicated in patients with one or more of the following sites of involvement: paranasal sinus, testicular, parameningeal, peri-orbital, CNS, paravertebral, bone marrow (with large cells) or in high risk disease. It is also indicated in the case of HIV-associated lymphoma.

Treatment

Treatment options for DLBCL differ between patients with localized (Ann Arbor stage I-II) and advanced (Ann Arbor stage III-IV) disease.[134,135] Prognosis is extremely good 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).

Doxorubicin-based chemotherapy (3 cycles) followed by RT produces excellent long-term outcomes in patients with limited-stage DLBCL (60 years or younger with no adverse risk factors).[136] In the SWOG 8736 study, patients with localized aggressive NHL, treated with CHOP (3 cycles) followed by RT had significantly better PFS (77% vs. 64% for CHOP alone) and OS 82% vs. 72% for CHOP alone) at 5-year follow-up; however, this difference disappeared with further follow-up.[137] Recently, ECOG study (E1484) showed that the addition of RT to CHOP (8 cycles) prolonged disease-free survival in patients who had achieved CR to CHOP alone.[138]

The efficacy of rituximab combined with CHOP (3 cycles) plus RT has also been reported in patients with limited stage DLBCL.[139] PFS at 2 years was 94% for patients treated with R-CHOP plus RT, which was favorable in historical comparison to the PFS observed for CHOP plus RT (85%). However, recent studies from Europe have questioned the role of radiation as reviewed by Fisher etal.[134] In a randomized comparison of CHOP (4 cycles) with and without radiation in older patients, the combined modality arm was inferior. In GELA study, ACVBP regimen was found to be superior to CHOP plus RT. However, this regimen includes vindesine which is not available in the United States.

CHOP chemotherapy has been the standard treatment for patients with stage II bulky or stage III-IV DLBCL. Rituximab has been added to CHOP chemotherapy to improve outcomes in patients with advanced DLBCL. In the GELA study, 399 elderly patients (60 -80 years) with untreated advanced DLBCL were randomized to receive 8 cycles of CHOP or R-CHOP. Long-term results of this study showed that event-free survival, PFS, disease-free survival, and OS were statistically significant in favor of R-CHOP, with a median follow-up of 5 and 7 years, in both low and high-risk patients. [140,141,142] These findings

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have been confirmed in three additional randomized trials including the MabThera International Trial (MInT) which extended the findings to young patients with favorable disease, the HOVON study and the ECOG/CALGB study confirmed the findings in patients older than 60.[143,144,145] Dose dense CHOP (CHOP-14) was found to be superior to standard CHOP-21.[146,147] Rituximab added benefit to CHOP-14 compared to CHOP-14 alone. In this study, OS significantly favored 6 cycles of R-CHOP-14 over 8 cycles because of late, non-cancer related deaths.[148] An ongoing study is evaluating the role of R-CHOP-14 versus R-CHOP-21. In phase II studies the dose-adjusted-EPOCH-R regimen has been shown to overcome certain risk features such as high proliferation rate,[149] and a randomized comparison with R-CHOP-21 is ongoing.

R-CHOP combined with RT is recommended for patients with localized disease. IFRT is recommended for patients who are not candidates for chemotherapy. Patients with non-bulky localized disease are treated with a full course (6-8 cycles) or an abbreviated course of R-CHOP (3 cycles), combined with locoregional RT. In patients with adverse risk factors, RT is optional if they are treated with 6-8 cycles of R-CHOP. Patients with no adverse factors can be treated with 6-8 cycles of R-CHOP alone, when RT is contraindicated because of clinical considerations. Patients who present with bulky disease may be more effectively treated with 6-8 cycles of R-CHOP and locoregional RT (category 1).

Patients (low- or high-intermediate risk) with advanced disease (stage III-IV) are treated with a full course (6-8 cycles) of R-CHOP-21. R-CHOP chemotherapy with rituximab is preferable due to reduced toxicities; however, other comparable anthracycline-based regimens are acceptable. In selected cases, RT to bulky sites may be beneficial. Suggested alternate treatment options include dose dense R-CHOP14 and dose adjusted-EPOCH-R (dose adjusted -etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin with rituximab), both of which are listed as category 2B recommendations. In addition, first-line consolidation with HDT/ASCR is also an option for eligible patients, though there is no consensus on the value of this approach. 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.

Patients who are receiving induction therapy should undergo evaluation prior to receiving RT, including all positive studies, after 3-4 cycles of chemotherapy. This interim restaging is performed to identify patients whose disease has not responded or has progressed despite induction therapy. Functional imaging (PET scans) may be particularly useful in determining whether residual masses represent fibrosis or viable tumor. If PET scan is positive, repeat biopsy of residual masses is recommended, before changing the treatment course. Interim PET scan can produce false positive results and should be done in the context of clinical trials, if clinically indicated, for possible primary refractory disease. End of treatment restaging is performed upon completion of induction therapy. The exact timing for end of treatment restaging is not known. The panel recommends that it is beneficial to wait for 8 weeks after completion of therapy before repeating PET scans.

After interim staging, the planned course of treatment is completed for all patients having CR and patients with stage III-IV disease with PR. Consideration of autologous stem cell rescue or completing the course of therapy with a higher dose of RT is recommended for patients with localized disease (stage I-II) with PR. In addition, appropriate clinical trial is recommended for all the PR patients. If there is no response to

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treatment or progressive disease is observed, patients are treated as described below for relapsed or refractory disease. RT may be given to selected patients with progressive disease and who are not candidates for chemotherapy. After end of treatment restaging, patients with CR to induction therapy are followed-up at regular intervals. Those with PR or progressive disease will be treated as described below for relapsed or refractory disease.

HDT/ASCR is the treatment of choice for patients with relapsed or refractory disease.[150, 151,152] Several chemotherapy regimens have been used as second-line therapy prior to HDT/ASCR; however, none of these have emerged as a preferred regimen.[153-158] Patients who achieved a CR to second-line therapy had a superior OS to that of patients who achieved a PR (65% v 30%).[155] Rituximab as a single agent was significantly active in patients with relapsed or refractory DLBCL.[159] However, limited data is available on the use of rituximab in combination with chemotherapy in such patients. Recent data from a phase II study showed that rituximab in combination with ifosfamide, carboplatin and etoposide (ICE) produced a CR rate of 53% in patients with relapsed or refractory DLBCL, which is significantly better, in historical comparison with the response rates observed for such patients treated with ICE alone (27%).[160] In an outpatient setting, rituximab with ICE produced an overall response rate of 71% (25% CR and 46% PR) and an estimated one-year event-free survival rate of 60% in patients with refractory B-cell lymphoma.[161] Rituximab with other regimens (DHAP, EPOCH and MINE) was also effective in patients with relapsed or refractory DLBCL. [122,162,163]

Patients with relapsed or refractory disease who are candidates for high-dose chemotherapy should be treated with second-line chemotherapy with or without rituximab. Suggested regimens listed in BCEL-B include the following: ICE, DHAP, GDP (gemcitabine, dexamethasone, cisplatin); MINE (mitoxantrone, ifosfamide, mesna, etoposide); miniBEAM (carmustine, etoposide, cytarabine, melphalan) and ESHAP (methylprednisolone, etoposide, cytarabine, cisplatin). Patients with CR or PR to second-line chemotherapy regimen should be considered for further consolidation with HDT/ASCR (category 1 for CR following relapse). 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 rescue is another option. Patients who achieve complete remission and are not eligible for high-dose therapy can be treated with single agent rituximab or multiagent chemotherapy regimens such as EPOCH, CEPP (cyclophosphamide, etoposide, prednisone, procarbazine)[164] with or without rituximab, or a low dose oral chemotherapy regimen such as PEPC (prednisone, etoposide, procarbazine, cyclophosphamide).[165] Patients with disease relapse following HDT/ ASCR should be treated in the context of a clinical trial or individually. However, those with progressive disease after three successive regimens are unlikely to derive additional benefit from currently available chemotherapy regimens, except for patients with a long disease-free interval.

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Burkitt Lymphoma and Lymphoblastic Lymphoma

Burkitt lymphoma (WHO classification) and precursor T and B lymphoblastic lymphomas have in common an exponential growth rate, a tendency to disseminate to the bone marrow and meninges, and characteristics overlapping those of acute lymphocytic leukemia. Burkitt lymphomas are rare and aggressive B-cell tumors typically involving extranodal disease sites. The vast majority (90%) of lymphoblastic lymphoma is a T-cell malignancy that occurs most often in young men and typically presents in the mediastinum. Tumor lysis syndrome (TLS) is more common in patients with Burkitt and lymphoblastic lymphoma. Initial treatment should include prophylaxis and monitoring for TLS

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Diagnosis

The typical immunophenotype of Burkitt lymphoma is sIg+, CD10+, CD19+, CD 20+, CD22+ TdT-, Ki67+ (100%), bcl-2-, bcl-6+. Most cases (80%) of Burkitt lymphoma have a translocation of c-myc from chromosome 8 to the immunoglobulin (Ig) heavy chain region on chromosome14 [t(8;14)].[166] Other variants [t(8;22) or t(2;8)] are less common. Immunophenotyping studies are essential to distinguish between the precursor T and B cell lymphoblastic lymphoma. Typical immunophenotypes of lymphoblastic lymphoma include dim expression of slg, CD10+, CD19+, CD20-/+, TdT+ for precursor B-cell lymphomas; Precursor T-cell lymphomas are characterized by dim expression of slg, CD 10-, CD1a+/-, CD2+, CD3-/+, CD4/8+/+, CD7+, CD19/20-, TdT+.

Workup

The initial diagnostic workup for these highly aggressive lymphomas includes imaging studies of the chest, abdomen, and pelvis, and a workup similar to that for acute lymphocytic leukemia. Bone marrow aspiration, biopsy, and lumbar puncture are essential. In these highly aggressive lymphomas, as in diffuse large-cell lymphomas, the serum LDH level has prognostic significance. Because Burkitt lymphomas are frequently associated with HIV infection, HIV serology should be part of the diagnostic workup for these diseases. These tumors exhibit a high degree of cellular proliferation, as determined by Ki67 staging, and frequent 8q translocations.

Treatment

Burkitt Lymphoma

In recent years, the treatment of Burkitt lymphoma with intensive short-course chemotherapy has been successful. 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.[167] In an international phase II study, CODOX-M regimen was associated with a 2-year OS of 81.5% in low-risk patients and, high risk patients treated with CODOX-M alternating with IVAC had a 2-year OS of 69.9%.[168] Modified CODOX-M regimen was also effective and well tolerated in elderly patients with Burkitt or Burkitt like lymphomas.[169] In another phase II trial, R-hyper-CVAD (hyper fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone and rituximab) alternating with R-MA (rituximab, methotrexate, cytarabine) [170]

Patients with Burkitt lymphoma with completely resected abdominal lesions or a single extra-abdominal mass and normal LDH level are considered to be at low-risk. Options for induction therapy for Burkitt lymphoma include clinical trial or combination chemotherapy regimens with or without rituximab. Disease relapse after 2 years is rare following CR to induction therapy, and follow-up should be individualized according to patient's characteristics. Patients with relapsed or refractory disease should be treated in the context of a clinical trial whenever possible.

Lymphoblastic Lymphoma

Lymphoblastic lymphoma has generally been treated with regimens appropriate for acute lymphoblastic leukemia (ALL), such as CALGB ALL regimen (dose-intensive cyclophosphamide and anthracycline, standard-dose vincristine and asparaginase, and intrathecal chemotherapy).[171] Other novel regimens listed in BLAST-A have also shown encouraging results. The combination of cytarabine and high-dose mitoxantrone, including intrathecal methotrexate was found to be superior to the standard vincristine and prednisone-based regimens when used induction therapy in adult patients with ALL.[172,173] In a study conducted by M.D. Anderson Cancer Center, hyperCVAD regimen produced 91% CR in patients with lymphoblastic lymphoma.[174]

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The 3-year PFS (66%) and OS (70%) compared favorably with the previously published results for ALL regimens. Two short intensive regimens containing rituximab (high-dose methotrexate with rituximab, and high-dose cytarabine with rituximab) have also shown promising results in ALL therapy.[175]

Patients with stage I-IV disease can be treated with any one of the regimens listed in BLAST-A or they can be treated in clinical trials. Poor risk patients can be considered for high dose therapy with autologous or allogeneic stem cell rescue. The use of maintenance chemotherapy is variable at NCCN institutions, with some institutions using up to 2 years of maintenance and others not using maintenance therapy. Enrollment in clinical trials is encouraged to refine these approaches and the most appropriate therapy should be chosen in consultation with an expert in lymphoma.

AIDS-Related B-Cell Lymphoma

Overview

AIDS-related lymphomas (ARL) are a heterogeneous group of tumors. Burkitt lymphoma and DLBCL are the most common forms of ARLs. The patients who develop Burkitt lymphoma generally have good CD4 counts though a small fraction may present with CD4 counts less than100. Primary CNS lymphoma (PCNSL) develops in patients with very low CD4 counts and is most often seen in uncontrolled AIDS. DLBCL occur in the patients between these extremes. In the era of highly active antiretroviral therapy (HAART), the incidence of HIV-associated lymphoma has fallen.[176] Overall, patients with HIV-associated lymphoma present with higher risk disease than matched patients with NHL without AIDS.[177]

Diagnosis

The diagnostic evaluation of HIV-associated lymphoma is not different from the non-HIV-associated disease. The major factor is to distinguish between Burkitt lymphoma and DLBCL. Hodgkin's disease and indolent lymphoma can also be seen in HIV patients but are distinctly less common.

Workup

The diagnostic evaluation is as outlined above for DLBCL or Burkitt lymphoma. However, all patients should have a lumbar puncture to rule out CNS involvement. In addition, baseline values for CD4 counts and viral load should be obtained.

Treatment

Optimal management of HIV-associated lymphoma is not established. Several key features have emerged as being critically important. Most studies that have found good long-term results have included the early introduction of HAART. Improved immune function with HAART has led to the evaluation of several chemotherapy regimens in patients with ARLs.[178] Combination chemotherapy regimens such as CHOP or CDE (cyclophosphamide, doxorubicin and etoposide) given with concomitant HAART,[179,180,181] or EPOCH regimen (etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin) without HAART,[182] have proven to be effective and tolerable in patients with ARL. In a retrospective analysis, HIV-positive patients with Burkitt lymphoma treated with CODOX-M/IVAC had outcomes similar to that observed in HIV-negative patients treated with the same regimen.[183] In a recent study, Mounier et al reported that HIV score, IPI (international prognostic index) score, and HAART affect survival in patients with ARL but not the intensity of the CHOP-based chemotherapy.[184] The role of

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HAART and dose-intensive chemotherapy for the treatment of ARLs remains controversial.

The NCCN guidelines recommend CODOX-M alternating with IVAC, dose-adjusted EPOCH or CDE (cyclophosphamide, doxorubicin and etoposide) for AIDS-related Burkitt lymphoma patients with CD4 count greater than 100. All other patients are treated with CHOP chemotherapy with or without high-dose methotrexate (not exceeding 3 g/m^2). Patients with AIDS-related DLBCL should be treated with dose-adjusted EPOCH, CDE or CHOP. Though the outcome in DLBCL is inferior to non-HIV patients, a significant portion of patients derive long-term benefit. Patients should be treated with full dose chemotherapy with growth factor support. Prophylactic therapy with intrathecal chemotherapy has also emerged as an important component of care. Rituximab appears to increase the risk of neutropenia and infection and there is no net benefit in patients with HIV-associated lymphoma.[185] The omission of rituximab is strongly suggested for DLBCL patients with CD4 counts of less than 50 due to the higher risk of infectious toxicities.[186]

PCNSL is associated with severe immunosuppression and poor prognosis. High-dose methotrexate, RT or antiretroviral therapy can be considered for patients with PCNSL.

T-Cell Lymphomas

Peripheral T-Cell Lymphomas

Overview

Peripheral T-cell lymphoma (PTCL) is heterogeneous group of lymphoproliferative disorder arising from mature T-cells of post-thymic origin.[187] In the REAL-WHO classification, PTCLs are divided into three groups: predominantly leukemic, nodal and extranodal. Predominantly nodal PTCL are further divided into three subtypes: PTCL-not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AILT) and anaplastic large cell lymphoma (ALCL).

PTCL-NOS is the most common subtype of PTCL. It is most often nodal, however, many patients present with extranodal involvement including the liver, bone marrow, GI tract and skin. PTCL-NOS is associated with poor OS and event free survival (EFS) rates compared to B-cell lymphomas.[188,189,190]

AILT presents with generalized lymphadenopathy, often with associated hepatomegaly or splenomegaly, hypergammaglobulinemia, eosinophilia, skin rash and fever. It occurs mainly in older patients. Prognosis is poor, with most series reporting an 5-year OS of 30% and PFS of only 13%.[189] In the most recent report from the GELA study, which included the largest series of patients with AILT, five and seven-year OS rates were 33% and 29% respectively, reaching an apparent plateau around 6 years.[191] The corresponding event free survival rates were 29% and 23% respectively.

ALCL 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-1 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.[192] The majority of patients ALCL present with advanced stage III or IV disease (64% for ALK-1 positive and 58% for ALK-1 negative) frequently associated with systemic symptoms and extra nodal involvement.[192,193] Systemic ALK-1 positive ALCL predominantly occurs at younger age and has a good prognosis compared to ALK-1 negative ALCL, which occurs in

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older patients. Five-year overall survival following anthracycline-based therapy was 79% for ALK-positive ALCL compared to 46% for ALK-negative ALCL.[194] Recent survival analysis from the International-T-cell lymphoma project also reported similar outcomes. However, in this report FFS or OS rates were similar in those patients with early stage ALK-positive or ALK-negative ALCL. ALK-negative ALCL patients had a modestly superior outcome compared to those with PTCL-unspecified. Primary cutaneous variant of ALCL is noted for the absence of ALK-1 protein and indolent course characterized by frequent relapses, generally confined to the skin, and very good long-term survival despite cutaneous relapses.

Staging and Prognosis

Staging is similar to that of the other aggressive NHLs. Recently, the Italian Intergroup for lymphoma proposed a new prognostic index for PTCL-NOS (PIT).[190] Risk factors include age older than 60 years, elevated LDH levels, performance status of 2 or more, stage III or higher with bone marrow involvement. Five-year overall survival was only 32.9% for patients with two risk factors and 18.3 % for those with three or 4 risk factors. In the NCCN guidelines, patients with stage I-II diseases are stratified into two groups (low intermediate risk and high intermediate risk) based on the age-adjusted prognostic index (aaPI).

In a retrospective GELA study, the prognoses of PTCL (including all subgroups) patients were compared with B-cell lymphoma patients with similar characteristics.[188] The complete response rates were 63% and 54% for patients with B-cell lymphoma and PTCL respectively. Five-year overall survival (OS) rate was also slightly better for patients with B-cell lymphomas (53%) compared to 41% for patients with PTCL. The 5-year EFS rates were 45% and 32% for B-cell and PTCL patients respectively. The difference in 5-year OS rates were more pronounced in patients with 2 or 3 adverse risk factors as determined by IPI (36% and 23% respectively for PTCL; 53% and 35% respectively for B-cell lymphomas). Initial characteristics and prognostic features were analyzed in another retrospective study in 174 patients with PTCL. Most patients were treated with anthracycline-based regimens.[195] The overall complete response rates (69% vs. 45%) and median survival (65 months vs. 20 months) were better for ALCL subgroup compared to PTCL.

Diagnosis

Diagnosis of PTCL is similar that described for other lymphomas, requiring adequate immunophenotyping to distinguish PTCL from B-cell neoplasms. The initial paraffin panel for immunohistochemical studies may only include Pan T-cell markers and can be expanded to include antibodies of T-cell lymphoma is suspected. Additionally, PTCL is often associated with clonal rearrangements of the receptor genes that may be seen in non-cancer T-cell diseases. Molecular and cytogenetic analysis can further clarify the T-cell origin of the lymphoma.

PTCL-NOS has variable T-cell associated antigens and lacks B-cell associated antigens. Majority of the nodal cases are CD4+ and CD8-.[196] Systemic ALCL has a strong expression of CD30. Evaluation of ALK-1 status, either based on immunophenotyping or genetic analysis of the t(2;5) or variant chromosomal rearrangements, is extremely important to identify the ALK-1 positive tumors that have a better prognosis. AILT cells express T-cell associated antigens and are usually CD4+. Recently, expression of CXCL13 has been identified as a useful marker in distinguishing AILT from PTCL-NOS.[197,198] It is also characterized by the presence of Epstein-Barr virus (EBV)-positive B-cells. EBER (EBV-encoded RNA) is positive in about 40% of PTCL and some case series have reported that EBER positive tumors have a

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worse prognosis. Evaluation of EBV status may also help characterize AILT.[196]

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, physical exam, and imaging studies, as indicated. MUGA scan or echocardiogram is also recommended, since chemotherapy is usually anthracycline based. In selected cases, HIV and HTLV-1 (human T-cell lymphoma virus) may be useful.

Treatment

PTCLs are less responsive to standard chemotherapy regimens 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.[199,200] However, it has not been possible to assess the impact of chemotherapy in this subgroup of patients with PTCLs due to small sample size. There have been no randomized studies comparing the chemotherapy regimens exclusively in patients with PTCL. Since there is no standardized treatment for PTCL, clinical trials are the preferred treatment option for all patients with PTCL, and essential to advancing our treatments form these diseases.

CHOP chemotherapy is the most commonly used first-line regimen for patients with PTCL. However, with the exception of ALK+ ALCL, outcomes are disappointing. In the International PTCL clinical and pathologic review project, anthracycline-based chemotherapy was associated with poor outcome in all patients, except for those with one or no risk factors. The inclusion of an anthracycline did not appear to favorably impact survival in this retrospective study. CHOP chemotherapy is frequently curative in only the small number of patients with favorable prognostic features.[201] In a retrospective study conducted by the British Columbia cancer agency, five-year OS rates were higher (64%) in low risk group compared to only 22% in high-risk group, in patients with PTCL treated with CHOP or CHOP-like chemotherapy.[189] ALK-positive ALCL patients had superior outcome compared to ALK- negative ALCL patients (5-year OS: 58% vs. 34% respectively). Chemotherapy regimens that are more intensive than CHOP did not show any significant improvement in the overall survival in patients with PTCL, with the exception of ALCL.[202]

The poor results with conventional chemotherapy have led many to explore the role of HDT/ASCR as a first-line consolidation therapy. Two prospective studies have demonstrated that HDT/ASCR as first-line consolidation improves treatment outcome in patients responding to induction therapy.[203,204] Both of these studies excluded patients with ALK-positive ALCL. In the prospective study conducted by the Gel-Tamo Study group, 19 out of 26 patients showing CR or PR to induction therapy with MegaCHOP received ASCR. At 2-year post-transplant follow-up, overall survival, progression-free survival and disease-free survival were 84%, 56% and 63% respectively.[203] Nordic lymphoma group evaluated induction therapy with CHOEP followed by ASCR in patients responding to induction therapy. Of the 77 evaluable patients, 58 (75%) patients underwent ASCR. At one-year post-transplant follow-up, 30 of the 39 patients were in complete remission.[204] Longer follow-up is necessary to evaluate the impact of first-line consolidation on time-to-treatment failure and overall survival. 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.

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AILT is a very 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.[205] The guidelines offer single agent corticosteroids as an initial treatment for AILT. However, given the poor prognosis for the majority, strong consideration should be given to treating these patients with approaches used for other PTCL.

Induction therapy with multiagent chemotherapy is recommended for all patients with PTCL-NOS or ALCL. In addition, patients with stage I-II disease (low-intermediate risk) are often effectively treated by adding adjuvant locoregional radiation therapy to involved region. Suggested regimens include CHOP, EPOCH or HyperCVAD alternating with methotrexate and cytarabine.

Following initial therapy, all patients undergo interim restaging by repeating all prior positive studies. If a PET scan is positive, rebiopsy is recommended before changing course of treatment. Patients are then divided into three groups according to treatment response (complete response, partial 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 (low-intermediate)

In patients showing complete response after interim restaging, planned radiation therapy is completed. First-line consolidation with HDT/ASCR is recommended for patients showing partial response at interim staging. Clinical trial including allogeneic transplant or radiation therapy 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 complete response. Patients with partial response 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 (high-intermediate) or stage III-IV

Patients with a complete response and ALK-1 positive ALCL need no further treatment. Those with ALK-1 negative ALCL, PTCL NOS or AILT with a complete response can be observed or they can be consolidated with HDT/ASCR. Patients with partial or no response or progressive disease after initial therapy are treated similarly to patients with relapsed or refractory disease.

Relapsed or Refractory Disease

Several studies have shown that second-line consolidation with HDT/ASCR produces similar outcomes patients with relapsed or refractory PTCL compared to those with B-cell lymphomas.[206-210] However, these studies are retrospective and in general only evaluated transplanted patients. Recent reports have shown the allogeneic transplantation may be an effective second-line therapy for patients with relapsed or refractory PTCL. In a phase II study, Corradini et al investigated the role reduced intensity conditioning (RIC) followed by allogeneic transplantation in patients with relapsed or refractory PTCL.[211] The estimated 3-year overall and progression-free survival rates were 81% and 64% respectively. Donor lymphocyte infusion induced responses in some patients progressing after allografting. Similar results were reported in a retrospective study from French national survey where majority of the patients were treated with myeloablative regimen.[212] Treatment related mortality was higher (30%) in this study compared to only 6% observed with RIC regimen.

Many new agents such as gemcitabine and denileukin diftitox have shown activity in small number of patients with relapsed or refractory

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PTCL.[213,214,215] Alemtuzumab produced a overall response rate of 36% in patients with relapsed or chemotherapy-refractory PTCLs.[216] But, it was associated with significant hematologic toxicity and infectious complications including deaths from opportunistic infections. Several other studies are evaluating alemtuzumab in combination with CHOP or CHOP-like chemotherapy.

Patients who are candidates for HDT/ASCR may be consolidated with second-line chemotherapy prior to transplant. Those with a complete or partial response can be considered for high dose therapy with allogeneic or autologous stem cell support. Patients who are non-candidates for high-dose therapy are treated with second line regimens for palliative intent only. Suggested treatments include alemtuzumab, bortezomib, gemcitabine and denileukin diftitox. Participation in a clinical trial is strongly preferred for these patients

Mycosis Fungoides and Sezary Syndrome

Cutaneous T-cell lymphomas (CTCLs) are a group of NHLs primarily developing in the skin and ultimately involve lymph nodes, blood and visceral organs. Mycosis fungoides (MF) and Sezary syndrome (SS) are the most common types of CTCLs. MF accounts for 60% of new cases of CTCL and SS occurs only to an extent of 5%. 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 and SS is characterized as an aggressive neoplasm.[217] However, a transformation to a large T-cell lymphoma has been documented a subgroup of patients and is diagnosed when there are more than 25% of large cells in a biopsy of an MF lesion.[218]

Staging

The TNM staging system developed by the mycosis fungoides cooperative group (MFCG) has been the standard for staging and classification of patients with MF and SS.[219] Recently, ISCL and EORTC recommended revisions to the MFCG staging system are based on the new data available in the area of immunohistochemistry, biology and prognosis of MF and SS since the publication of MFCG. In the revised staging system, all staged patients should have a definitive diagnosis of MF and SS.[220] T1 disease is defined as less than 10% of the skin surface involvement with patches or plaques and T4 disease is 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. Lymph node biopsy for staging is recommended only for clinically abnormal node (1.5 cm or larger in diameter). Visceral disease with the involvement of an organ other than the skin, nodes or blood should be documented using imaging studies. Blood involvement is classified into three groups: B0 is associated with the absence of significant blood involvement (5% or less of Sezary cells); B1 is defined as having a low tumor burden (more than 5% of Sezary cells but does not meet the criteria for B2); B2 is associated with high tumor burden with more than 1000 Sezary cells/μl. According to the updated staging system, patients with stage III are further divided into two subgroups IIIA and IIIB to differentiate the extent of blood involvement (B0 and B1 respectively).

Prognosis

The most significant prognostic factors of survival include patient's age at presentation, extent and type of skin involvement, overall stage (T-classification), presence or absence of extracutaneous disease and peripheral blood involvement.[221-224] Patients diagnosed with limited

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patch or plaque disease have an excellent prognosis, whereas those who have tumor stage disease or erythrodermic skin involvement have a less favorable prognosis and patients with who present with extracutaneous disease have a very poor prognosis. In a retrospective study involving 525 patients with MF and SS, the 5-year OS was significantly better (80% vs. 56%) for patients less than 57 years of age compared to that of patients 57 years or older.224 The risk of disease progression, development of extracutaneous disease or death due to MF was correlated with initial stage.

Diagnosis

In the algorithms developed by the International Society for Cutaneous Lymphoma (ISCL), the diagnosis of MF is based on integration of clinical, histopathologic, immunopathologic, and molecular biological characteristics.[225] According to the revised criteria, diagnosis of SS includes one of the following: an absolute Sézary cell count of 1000 cells/mm3 or more; CD4/CD8 ratio of 10 or higher caused by an increase in circulating CD4+ T cells and/or an abnormal immunophenotype including the significant loss of CD7 (>40%) or CD26 (>30%) by flow cytometry with evidence of a T-cell clone in the blood.[4]

Complete skin exam, 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 Sezary cells are recommended in the absence of a definitive skin diagnosis. MF and SS cells are characterized by CD2+, CD3+, CD4+, CD5+, CCR4+, CD45RO+ and they lack certain T-cell markers CD7 and CD26.[226] There are subtypes of MF that are also CD8+. If there is a histological evidence of large cell transformation 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. T-cell receptor (TCR) gene rearrangement should be interpreted with caution since TCR clonal rearrangements can also be seen in non-malignant conditions. TCR gene rearrangement analysis by polymerase chain reaction (PCR) is a useful technique to support the diagnosis of MF and SS, especially in distinguishing MF from inflammatory dermatoses.[227]

Work Up

The work-up of patients diagnosed with MF or SS involves complete skin examination to assess the extent of the disease, examination of lymph nodes or other masses for the evaluation of lympadenopathy or organomegaly. Laboratory studies should include CBC with Sezary screen and Sezary flow cytometry to assess for expanded CD4+ cells with increased CD4:CD8 ratio or with abnormal immunophenotype. Patients with T1 and limited T2 disease without adenopathy, blood involvement, or unfavorable features such as folliculotropic or large-cell transformation do not need any imaging tests other than a chest x-ray, while other patients should additionally undergo either CT or PET/CT scan of the neck/chest/abdomen and pelvis. Integrated PET-CT was found to be more sensitive for the detection of lymph node involvement than CT alone and can help direct biopsies.[228] Bone marrow biopsy is not needed for staging of patients, but may be helpful in those with suspected marrow involvement or in those with an unexplained hematologic abnormality. TCRGR of peripheral blood lymphocytes is recommended if SS is suspected. Biopsy of suspicious lymph nodes is recommended with evaluation for T cell receptor gene rearrangements, especially due to the poor prognosis of patients with clonal rearrangement in lymph nodes.[229]

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Treatment alternatives for MF and SS

Initial treatment in patients with patch/plaque disease consists of skin-directed therapies (localized or generalized), with the addition of systemic biologic therapy for refractory, or progressive disease. Those patients who have unfavorable prognostic features (e.g., folliculotropic or large-cell transformed MF) may have systemic biologic 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.[230,231,232] 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, or topical bexarotene. 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.

Topical corticosteroids are effective especially for the treatment of patch-stage MF, producing a CR rate of over 90%.[233,234] However, long-term use of topical steroid may lead to skin atrophy or striae formation and the risk worsens with increased potency of the steroid. 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.[235,236] Long term follow-up results in 203 patients have confirmed the safety of topical therapy with nitrogen mustard.[237] The efficacy were similar for aqueous and ointment preparations, however, the ointment was associated with reduced toxicity. Patients with T1 disease had better response rates (93% vs. 72%) and survival outcomes (65% vs. 34%) than those with T2 disease. Freedom from progression (FFP) in T1 disease at 5 and 10 years were 92% and 85% respectively and in T2 disease FFP was 83% at 5 and 10 years. An ongoing multicenter trial is evaluating the efficacy of topical nitrogen mustard in patients with stage I or IIA MF.

Synthetic retinoids such as bexarotene have shown activity in patients with MF and SS. Bexarotene gel is the only FDA approved topical therapy for MF and SS. FDA approval was based on the data from two open-label, historically-controlled clinical studies involving 117 patients with CTCL.[238,239] In the phase I-II trial involving 67 patients with early stage MF, CR was attained in 21% and PR was observed in 42%.[238] Patients with no prior therapy responded at a higher rate than those who had received prior topical therapies. In the phase III multicenter study of 50 patients with early stage refractory MF, overall response rate was observed in 44% of patients with 8% of patients achieving CR.[239]

MF is extremely radiosensitive and RT is the most effective single agent for early stage MF.[240] TSEBT is effective especially 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 for T2 and T3 disease compared to mechlorethamine hydrochloride alone (76% vs. 44% for T2; 44% vs. 8% for T3).[241]

Phototherapy with UVB (including narrow-band) and photochemotherapy (PUVA) are effective alternative treatment options for patients with early stage MF.[242,243] In long-term follow-up studies, PUVA was associated with prolonged disease-free remissions.243 In a

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retrospective analysis, phototherapy with narrow-band UVB and PUVA produced comparable complete remission rate (81% vs. 71%), partial remission rate (19% vs. 29%) and relapse-free survival (24.5 months vs. 22.8 months) in patients with early stage MF.[244] However, cumulative doses of UV are associated with increased risk of UV-associated skin neoplasms. Thus, phototherapy may not be appropriate for patients with the 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

Systemic therapies with extracorporeal photopheresis (ECP), interferons, systemic retinoids, denileukin diftitox or vorinostat are preferred over traditional chemotherapy for patients who do not respond to initial skin-directed therapies. Multiagent chemotherapy is reserved only for patients who do not respond to single agent chemotherapy 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 immnunomodulatory therapy using psoralen and UVA radiation extracorporeally. It involves the removal of leukocytes by leukopheresis. The leukocytes are treated with 8-methoxypsoralen, exposed to UVA and returned to the patient. ECP is a long standing treatment of MF, and is particularly indicated in patients with or at risk of blood involvement (erythrodermic stage III disease or IVA with Sezary Syndrome).[245,246]

Interferons and retinoids [all-trans retinoic acid (ATRA) and isotretinoin (13-cis retinoic acid) have been used for many years for the treatment of CTCL.[247,248] Oral bexarotene has been evaluated for the treatment of refractory or persistent early and advanced stage CTCL in two multicenter clinical trials.[249,250] In early stage CTCL, bexarotene was well tolerated and effective in 54% of patients at doses of 300 mg/m2 per day.249 In advanced CTCL, clinical CR and PR were observed in 45% of patients receiving 300 mg/m2/d.[250] At more than 300 mg/m2/d, response rate was 55%, including 13% clinical CR. Side effects were reversible and manageable with appropriate medications prior to initiation of treatment. Bexarotene capsules received FDA approval in December, 1999 for the treatment of refractory CTCL. In retrospective comparison, ATRA and bexarotene had similar efficacy in the treatment of patients with relapsed MF and SS.[251]

Denileukin diftitox is a recombinant fusion protein with interleukin-2 (IL-2) and diphtheria toxin, and targets the high-affinity interleukin-2 receptor (CD25) expressed on malignant T-cells and B-cells. In a phase III study, overall response rate was 30% with a median duration of 6.9 months in patients who have received other treatments.[252] Clinically significant improvement in self-rated overall QOL, skin appearance, and pruritus severity was observed in 68% of the patients who had significant pruritus at baseline. However, denileukin difititox is associated with significant side effects including hypersensitivity reactions and vascular leak syndrome. Myelosuppression is an uncommon side effect. Denileukin diftitox was approved in February, 1999 for the treatment of persistent or recurrent CTCL in patients whose malignant cells express CD25 component of IL-2 receptor.

Histone deacetylase (HDAC) inhibitors are a new class of drugs that are potent inducers of histone acetylation, cell cycle arrest and apoptosis. Activity and safety of vorinostat in patients with refractory CTCL was confirmed in a phase II trial.[253] In a phase IIB study involving 74 patients with persistent, progressive or refractory CTCL, overall

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response rate and median time to progression were 29.7% and 4.9 months respectively.[254] Median time to progression was greater than 9.8 months for stage IIB or higher responders. The response rates and median response durations were comparable to those obtained with bexarotene capsules and denileukin diftitox. Vorinostat was the first HDAC inhibitor to receive FDA approval in October 2006 for the treatment of patients with progressive, persistent, or recurrent CTCL, on or following two systemic therapies.

Systemic chemotherapy is used as a primary treatment only for advanced disease, or as second-line therapy for early stage disease that is refractory to skin-directed therapies and systemic biological therapies. Low dose methotrexate has been used to treat early stage MF and SS for many years, although there is not extensive literature documenting outcomes.[255,256] Gemcitabine as a single agent has also been effective in patients with advanced, heavily pretreated CTCL and as front-line therapy in untreated CTCL patients.[257,258] Pentostatin has shown activity either as a single agent or in combination with interferon alfa in patients with advanced MF or SS.[259,260] Anecdotal reports suggest activity for temozolomide and bortezomib.[261,262] Pegylated doxorubicin have also shown significant activity in patients with pretreated, advanced or refractory CTCL.[263]

Combination therapies

Combinations of biologic therapies as distinct from combination chemotherapies are used when single agent therapies fail or in advanced, progressive, refractory, or symptomatic disease. Several combination therapies have been studied in clinical trials for CTCL. Most commonly used combinations are phototherapy plus either interferon or systemic retinoid and ECP plus either IFN or systemic retinoid or both.[264-269] PUVA when used in combination with interferon alfa produced an overall response rate of 93% in patients with stage IB to stage IVB disease.[264] Median duration of response exceeded 25 months. In another prospective phase III trial, combination of low-dose interferon alfa and PUVA resulted in a CR rate of 84% in patients with early stage MF.[265] The addition of PUVA to the combination of ECP, interferon and bexarotene resulted in rapid sustained remission in patients with SS.[266] In a long-term follow-up study involving patients with advanced CTCL and poor prognostic factors, combined modality therapy (ECP with interferons and/or systemic retinoids) resulted in better response rates (84%) compared to ECP alone (75%).[267] Median survival (74 months vs. 66 months) was better for patients receiving combination therapy. Combination therapy was well tolerated. Combination of bexarotene with PUVA, ECP and/or interferon also resulted in higher response rates in patients with advanced disease.[268] Systemic retinoids have been studied in combination with other biological response modifiers in patients with advanced disease.[270,271] The combination of bexarotene and denileukin diftitox is particularly interesting since bexarotene has been shown to increase CD25 expression in CTCL cells and thereby increasing the susceptibility of T-cells to denileukin diftitox.

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Treatment based on Clinical Stage

Primary Treatment

Patients with Stage IA have an excellent prognosis using skin directed therapies alone. Stage IA is managed primarily with skin-directed therapies, alone or in combination with other skin-directed therapies including local RT. Treatment options include topical corticosteroids, nitrogen mustard or carmustine, bexarotene, phototherapy with UVB for patch or thin plaques or PUVA for thicker plaques. Patients with Stage IB-IIA disease require generalized skin treatment. Topical retinoids are not recommended for generalized skin involvement since they can cause a lot of irritation. In addition to the other skin-directed therapies

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used for Stage IA disease, TSEBT is another treatment option for those with severe skin symptoms or generalized thick plaque or tumor. 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. For patients with sites that are not responsive to generalized treatment, additional treatment may be needed.

Early stage disease (stage IA, stage IB-IIA) with blood involvement (B1) or histological evidence of folliculotropic or large cell transformation, are associated with less favorable outcome, thus, these patients may be best managed with more intense treatments as described for stage IIB limited disease or stage III with B1 involvement, respectively.

Patients with Stage IIB disease can be separated into two categories: limited extent tumor disease with or without patch/plaque disease or generalized tumor disease or limited extent tumor disease with blood involvement (B1) or large cell transformed MF. Patients with limited extent tumors can be managed with local radiation. Skin directed therapies, as described above for stage I-IIA disease can be used for the residual patch/plaque disease. Alternatively, they can also be treated with systemic therapy (SYST- CAT A) including ECP, systemic retinoids (bexarotene, ATRA or isotretinoin [13-cis-retinoic acid]), interferons, vorinostat, denileukin diftitox or low-dose methotrexate.

Patients with generalized tumor disease or limited extent tumor disease with blood involvement (B1) or large cell transformed MF are treated with TSEBT or systemic therapies, with or without adjuvant skin directed therapy. Suggested systemic therapy options include ECP, systemic retinoids (bexarotene, ATRA or isotretinoin [13-cis-retinoic acid]), interferons, vorinostat or denileukin diftitox, chemotherapy agents such as methotrexate, liposomal doxorubicin, gemcitabine (first-line therapy) and chlorambucil, pentostatin, etoposide, cyclophosphamide, temozolomide (second-line therapy).

Management of patients with stage III disease depends on the extent of blood involvement: no significant blood involvement (B0) or some blood involvement (B1), which is less than that observed for SS. Patients with no significant blood involvement are treated with generalized skin-directed therapies (similar to those recommended for stage IB -IIA) with or without systemic therapy (ECP, low dose methotrexate and other biological agents recommended for stage IIB disease). Safety data on the use of vorinostat in combination with phototherapy or RT is currently lacking. Generalized skin-directed therapies other than topical steroids may not be well tolerated for patients with stage III disease. Patients with stage III disease with significant blood involvement are treated mainly with ECP, low dose methotrexate or systemic biologic therapies as recommended above for those with no blood involvement. 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.

Stage IV disease includes SS (with or without lymph node involvement) and bulky lymph node or visceral (solid organ disease). SS patients are treated with singe agent systemic biologic therapy (ECP, systemic retinoids, interferons, vorinostat, denileukin diftitox or low dose methotrexate) or combination therapies. Suggested regimens for combination therapies are listed in MFSS-A. Bulky lymph node or solid organ disease is frequently managed with chemotherapy (SYST-CAT B) with or without RT and skin-directed therapy. SYST-CAT B agents in general have more rapid onset of responses and are more often used. In certain clinical circumstances SYST-CAT A agents or even RT alone

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may be used. Adjuvant biologic therapy may be considered following chemotherapy to improve response duration.

All patients (stage IA through stage IV) showing response 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 or Progressive Disease

Autologous stem cell transplantation (SCT) has been used infrequently for patients with CTCL. In general, the durations of response have been short thus limiting its usefulness. The use of allogeneic SCT in patients with advanced MF and SS has been reported only in case reports and small series.[272] Data on allogeneic SCT, particularly using non-myeloablative conditioning, suggest the existence of graft versus T- cell lymphoma effect and success with long term durable remissions has been reported in highly selected patients.[272] Alemtuzumab, anti-CD52 antibody has shown promising activity in patients with advanced MF and SS. However, it is also associated with significant toxicity.[273]

Systemic therapy (SYST-CAT A), 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. Skin-directed therapy can be used as adjuvant treatment to reduce skin symptoms. Patients who do not respond to treatment with SYST-CAT A agents are treated with single agent systemic chemotherapy (SYST-CAT B). Suggested agents are listed in MFSS-A. Allogeneic SCT may be considered for patients with stage IIB -IV disease that is progressive or refractory to multiple primary treatment options. Appropriate patients (stage IIB or greater MF who have failed multiple systemic therapies and adequate trial of skin-directed therapy or whose disease is not amenable to skin-directed therapy), may be referred for a transplant consultation. Ideal time for allogeneic SCT is when their disease is well controlled with induction therapy and before their disease has progressed to a state where the chance of response or survival with allogeneic SCT is low. 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. Alemtuzumab may be considered for patients with stage III-IV (specifically, SS) disease that is refractory to previous treatments.

Currently there is no definitive treatment for advanced disease that can produce reliable durable remissions or curative results, other than possibly, allogeneic SCT. The guidelines recommend participation in a clinical trial as a treatment option for all patients with relapsed or progressive disease.

Discussion
Updates in progress

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