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≠ Pathology
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These guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representations nor warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2007.
Summary of changes in the 2.2007 version of the Non-Hodgkin's Lymphoma guidelines from the 1.2007 version include:

New Guidelines were added for Mycosis Fungoides/Sezary Syndrome (MFSS-1).

New Guidelines were added for Peripheral T-Cell Lymphomas (TCEL-1).

Global Changes

Testing for Hepatitis B was added as "essential" to the work-up sections of all B-Cell Lymphomas.

Diagnostic and Workup sections were added for Gastric MALT, Nongastric MALT, Nodal Marginal Zone, and Splenic Marginal Zone Lymphomas.

The Response Criteria for Lymphoma was updated to include PET scan (NHODG-A 2 of 2).

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Suggested Treatment Regimens (CSLL-C 1 of 2) Rituximab was added to the first-line therapy options in combination with chlorambucil, cyclophosphamide, or CVP. Alemtuzumab for patients with 17p- mutation was added to the first-line therapy options. Footnotes b, e, and f are new to page.

Follicular Lymphoma

The statement "Histologic grading cannot be performed on an FNA" was added to the Diagnosis section under Essential (FOLL-1).

Footnote "d" was modified to include recommendations if radioimmunotherapy is considered (FOLL-1).

Footnote "p" is new to the page and footnote "q" was modified to include information regarding FDG uptake on PET (FOLL-2).

A diagram of the nodal sites mapping was added (FOLL-A).

Suggested Treatment Regimens (FOLL-B 1 of 2)

First- and second-line extended dosing with rituximab was added as a category 2B recommendation. Footnotes e, i, j, k, l are new to the page. First-line therapy options were added for the elderly or infirm.

Gastric MALT Lymphoma

Staging was added for Gastric MALT Lymphoma (MALT-A).

Nongastric MALT Lymphoma

Footnote c is new to the page. For Stage IE-II, the option RT for completely resected, negative margins was added (NGMLT-2).

Splenic Marginal Zone Lymphoma

For patients with cytopenias or symptoms, "preferred" was added to splenectomy and rituximab was added as optional (SPLN-1).

Mantle Cell Lymphoma

Suggested Treatment Regimens (MANT-A 1 of 2)

FMR was added as an option for second-line therapy and rituximab maintenance was added as an option in second-line therapy after FMCR.

Diffuse Large B-Cell Lymphoma

Footnote f is new to the page (BCEL-2).

Suggested Treatment Regimens (BCEL-B 1 of 2)

The RCHOP x 14 regimen was added as an option in first-line therapy with a category 3 designation. Rituximab was added as an option in combination with any of the listed regimens for second-line therapy. GDP was added as a treatment option in second-line therapy.

Burkitt's Lymphoma

Suggested Treatment Regimens (BURK-A 1 of 2)

High dose therapy with stem cell rescue was added as an option for patients in relapse.

Lymphoblastic Lymphoma

Suggested Treatment Regimens (BLAST-A 1 of 2)

The option for maintenance rituximab was added.

New Guidelines were added for Peripheral T-Cell Lymphomas (TCEL-1).
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 of a mass is not desirable for the initial diagnosis of lymphoma. However, in certain circumstances a combination of morphologic and flow cytometric studies may provide valuable information to provide a diagnosis. This is particularly true for the diagnosis of CLL.
- Adequate immunophenotyping to establish diagnosis
  - Paraffin panel: CD20 (L26/Pan B), CD3, CD5, CD23, cyclin D1 or
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10, CD38

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- Immunohistochemical studies
  - Frozen section panel: kappa/lambda, CD5, CD20
  - Paraffin panel: optional- CD43, CD10, CD79a, kappa/lambda
- Molecular genetic analysis to detect antigen receptor gene rearrangements
- Cytogenetics or FISH\textsuperscript{d} to detect t(11;14), 17p-, t(11q;v), del13q, +12
- Determination of CD38 and/or Zap 70\textsuperscript{d} expression by flow cytometry or immunochemistry\textsuperscript{e}

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

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- Quantitative immunoglobulins
- Reticulocyte count and direct Coombs’ test
- Chest/abdominal/pelvic CT (particularly when peripheral adenopathy is present)
- Beta-2-microglobulin
- Uric acid
- Chest x-ray (PA and LAT)
- Anti-platelet antibodies (category 2B)
- Unilateral bone marrow biopsy (± aspirate)
- Discussion of fertility issues and sperm banking

\textsuperscript{a}CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma.
\textsuperscript{b}Typical immunophenotype: CD5+, CD23+, CD43+/-, CD10-, CD19+, CD20 dim, and cyclin D1-. Note: Some cases may be CD23- or dim and some MCL may be CD23+; cyclin D1 immunohistochemistry or FISH for t(11;14) should be considered in all cases.
\textsuperscript{c}May be helpful to distinguish between benign and malignant B-cells in paraffin.
\textsuperscript{d}These are helpful in prognostic determination and can influence therapeutic decisions. See Prognostic Information for CLL (CSLL-A).
\textsuperscript{e}Evaluation of ZAP 70 expression can be challenging and is not universally available.

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CLL/SLL

**PRESENTATION**

- **SLL/Localized**
  - (Ann Arbor Stage I, II)
  - Locoregional radiotherapy or Observe

- **CLL or SLL**
  - (Ann Arbor Stage III, IV)
  - CLL Rai Good risk
  - CLL Rai Intermediate Risk
  - CLL Rai High Risk

**INDUCTION THERAPY**

- Consider prophylaxis for tumor lysis syndrome

Indications for treatment:
- Eligible for clinical trial
- Autoimmune cytopenia
- Recurrent infections
- Symptoms
- Threatened end-organ function
- Cytopenia(s)
- Bulky disease
- Steady progression
- Patient preference
- Histologic transformation

No indication → Observe

Indication present → See Suggested Regimens

CLL/C

CLL/C

**INDUCTION THERAPY**

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

- There are three forms of autoimmune cytopenias: autoimmune hemolytic anemia (AIHA), immune thrombocytopenic purpura (ITP), and pure red cell aplasia. Initial therapy for AIHA and ITP is steroids. Intravenous immunoglobulin (IVIG) may be used in refractory cases. Rituximab or splenectomy are an option in selected AIHA/ITP patients. In cases of pure red cell aplasia, testing for parvovirus is indicated. The therapy for pure red cell aplasia may include immunosuppressive agents such as prednisone, cyclosporine and ATG.

- Treatment with IVIG, if hypogammaglobulinemic.

- The diagnosis of histologic transformation requires areas of clear-cut DLBCL or Hodgkin's lymphoma. If there is clinical suspicion of transformation, consider management as per FOLL-4.

- When Absolute Lymphocyte Count (ALC) > 25,000 cells/mm³, rituximab should be eliminated for the first cycle of therapy or should be administered using a split dosing schedule (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(1):6-14).

See Response after Therapy (CSLL-3)
**RESPONSE AFTER INDUCTION THERAPY**

<table>
<thead>
<tr>
<th>Complete response</th>
<th>Clinical trial or Observe</th>
<th>Progressive disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>or partial response</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ADDITIONAL THERAPY**

Indications for treatment:
- Eligible for clinical trial
- Autoimmune cytopenia
- Recurrent infections
- Symptoms
- Threatened end-organ function
- Cytopenia(s)
- Bulky disease
- Steady progression
- Patient preference
- Histologic transformation

**Indication present**

**See Suggested Regimens (CSLL-C)**

**Indication not present**

**Observe**

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**h** There are three forms of autoimmune cytopenias: autoimmune hemolytic anemia (AIHA), immune thrombocytopenic purpura (ITP), and pure red cell aplasia. Initial therapy for AIHA and ITP is steroids. Intravenous immunoglobulin (IVIG) may be used in refractory cases. Rituximab or splenectomy are an option in selected AIHA/ITP patients. In cases of pure red cell aplasia, testing for parvovirus is indicated. The therapy for pure red cell aplasia may include immunosuppressive agents such as prednisone, cyclosporine and ATG.

**i** Treatment with IVIG, if hypogammaglobulinemic.

**j** The diagnosis of histologic transformation requires areas of clear-cut DLBCL or Hodgkin's lymphoma. If there is clinical suspicion of transformation, consider management as per FOLL-4.

**k** When Absolute Lymphocyte Count (ALC) > 25,000 cells/mm³, rituximab should be eliminated for the first cycle of therapy or should be administered using a split dosing schedule (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(1):6-14).

**l** See Response Criteria: CLL (CSLL-D) or SLL (NHODG-A).

**m** Length of treatment is clinically based, though 4-8 cycles is most commonly used among NCCN institutions.
PROGNOSTIC INFORMATION FOR CLL\(^a\)

Immunoglobulin Variable Gene Mutation and Surrogates by Flow

<table>
<thead>
<tr>
<th></th>
<th>Outcome Association</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Favorable</td>
</tr>
<tr>
<td>DNA sequencing</td>
<td></td>
</tr>
<tr>
<td>(V_H)</td>
<td>&gt; 2% mutation</td>
</tr>
<tr>
<td>Flow Cytometry</td>
<td></td>
</tr>
<tr>
<td>ZAP70 (&gt; 20% leukemic cells)</td>
<td>Negative</td>
</tr>
<tr>
<td>CD38 &gt; 30%</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Interphase Cytogenetics (FISH)

<table>
<thead>
<tr>
<th></th>
<th>Unfavorable</th>
<th>Neutral</th>
<th>Favorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(11q;v)</td>
<td></td>
<td>Normal</td>
<td>del13q (as a sole abnormality)</td>
</tr>
<tr>
<td>17p-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+12</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)This provides useful prognostic information without guiding therapeutic decisions. However, 17p- is associated with resistance to fludarabine, alkylators and possibly rituximab though activity of alemtuzumab has been anecdotally reported.

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### CLL Staging Systems

#### Rai System<sup>a</sup>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Risk Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Lymphocytosis, lymphocytes in blood &gt; 15,000/mcL and &gt; 40% lymphocytes in the bone marrow</td>
<td>Good</td>
</tr>
<tr>
<td>I</td>
<td>Stage 0 with enlarged node(s)</td>
<td>Intermediate</td>
</tr>
<tr>
<td>II</td>
<td>Stage 0-I with splenomegaly, hepatomegaly, or both</td>
<td>Intermediate</td>
</tr>
<tr>
<td>III&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Stage 0-II with hemoglobin &lt; 11.0 g/dL or hematocrit &lt; 33%</td>
<td>High</td>
</tr>
<tr>
<td>IV&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Stage 0-III with platelets &lt; 100,000/mcL</td>
<td>High</td>
</tr>
</tbody>
</table>

#### Binet System<sup>b</sup>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Hemoglobin ≥ 10 g/dL and Platelets ≥ 100,000/mm&lt;sup&gt;3&lt;/sup&gt; and &lt; 3 enlarged areas</td>
</tr>
<tr>
<td>B</td>
<td>Hemoglobin ≥ 10 g/dL and Platelets ≥ 100,000/mm&lt;sup&gt;3&lt;/sup&gt; and ≥ 3 enlarged areas</td>
</tr>
<tr>
<td>C&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Hemoglobin &lt; 10 g/dL and/or Platelets &lt; 100,000/mm&lt;sup&gt;3&lt;/sup&gt; and any number of enlarged areas</td>
</tr>
</tbody>
</table>

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<sup>a</sup>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.


<sup>c</sup>Immune-mediated cytopenias are not the basis for these stage definitions.

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SUGGESTED TREATMENT REGIMENS
(in alphabetical order)

Chemotherapy - single and combination therapy

First-line Therapy
- Alemtuzumab for patients with 17p- mutation
- Chlorambucil (pulse or continuous) ± prednisone ± rituximab
- Cyclophosphamide ± prednisone ± rituximab
- CVP (cyclophosphamide, vincristine, prednisone) ± rituximab
- FC (fludarabine, cyclophosphamide) ± rituximab
- Fludarabine ± rituximab

Second-line Therapy
- Alemtuzumab
- PC (pentostatin, cyclophosphamide) ± rituximab
- Chemotherapy (as above) ± rituximab or alemtuzumab

See references for regimens CSLL-C 2 of 2.

When Absolute Lymphocyte Count (ALC) > 25,000 cells/mm³, rituximab should be eliminated for the first cycle of therapy or should be administered using a split dosing schedule (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(1):6-14).

Consider prophylaxis for tumor lysis syndrome.

Prophylactic therapy for shingles and pneumocystis should be considered in purine analog-based combination therapy.

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 weeks. Consultation with an Infectious Disease expert may be necessary.

The use of purine analogs has been associated with the development of autoimmune hemolytic anemia (AIHA) and clinicians should use caution using purine analogs in patients with AIHA.

Rituximab and alemtuzumab should be used in combination only when there is existing literature to support its use in combination.

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SUGGESTED TREATMENT REGIMENS

REFERENCES

Chlorambucil

Fludarabine/cyclophosphamide

Fludarabine + rituximab

Alemtuzumab

Pentostatin/cyclophosphamide
# RESPONSE CRITERIA FOR CLL<sup>a</sup>

<table>
<thead>
<tr>
<th></th>
<th>Complete response</th>
<th>Partial response&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Progressive disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical exam (including nodes, liver, spleen)</td>
<td>Normal</td>
<td>≥ 50 % decrease</td>
<td>≥ 50 % increase or new</td>
</tr>
<tr>
<td>Symptoms</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytes (x 10&lt;sup&gt;9&lt;/sup&gt;/L)</td>
<td>≤ 4</td>
<td>≥ 50 % decrease from pretreatment baseline value</td>
<td>&gt; 50 % increase in circulating lymphocytes</td>
</tr>
<tr>
<td>Neutrophils (x 10&lt;sup&gt;9&lt;/sup&gt;/L)</td>
<td>≥ 1.5</td>
<td>≥ 1.5 or 50 % improvement over baseline</td>
<td></td>
</tr>
<tr>
<td>Platelets (x 10&lt;sup&gt;9&lt;/sup&gt;/L)</td>
<td>&gt; 100</td>
<td>&gt; 100 or 50 % improvement over baseline</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>&gt; 11 (untransfused)</td>
<td>&gt; 11 or 50 % improvement over baseline (without transfusions)</td>
<td></td>
</tr>
<tr>
<td>Bone marrow lymphocytes (%)</td>
<td>&lt; 30; no nodules</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Duration ≥ 2 mo</td>
<td>Duration ≥ 2 mo</td>
<td>Richter’s syndrome</td>
</tr>
</tbody>
</table>

<sup>a</sup>This research was originally published in Blood. Cheson BD, Bennett JM, Grever M, et al. National Cancer Institute-sponsored Working Group guidelines for chronic lymphocytic leukemia: revised guidelines for diagnosis and treatment. Blood 1996;87(12):4990-7. (c) the American Society of Hematology.

<sup>b</sup>The patient must exhibit ≥ 50% decrease in peripheral blood lymphocytes from pretreatment baseline value and ≥ 50% reduction in lymphadenopathy and/or ≥ 50% reduction in the size of the liver and/or spleen (if abnormal prior to therapy), as well as one or more of the remaining features.

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Follicular Lymphoma (grades 1-2)

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 alone is not desirable for the initial diagnosis of lymphoma. In certain circumstances a combination of morphologic and flow cytometric studies may provide adequate information to provide a diagnosis. Histologic grading cannot be performed on a FNA.
- Adequate immunophenotyping to establish diagnosis:
  - Paraffin Panel: CD20 (L26/Pan B), CD3, CD5, CD10, CD21, CD23, bcl-2
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- Immunohistochemical studies
  - Frozen Section Panel: kappa/lambda, CD5, CD20
  - Paraffin panel: bcl-6, cyclin D1 (if CD 10- and/or CD5+ or CD43+), CD43, kappa/lambda, CD21, MIB1(Ki-67)
- Molecular genetic analysis to detect antigen gene receptor rearrangements; bcl-2 rearrangement
- Cytogenetics or FISH for t(14;18)

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
- Hepatitis B testing

USEFUL IN SELECTED CASES:
- Bone marrow biopsy + aspirate, essential to document clinical stage I-II disease
- Neck CT
- Beta-2-microglobulin
- PET scan (preferred) or Gallium-67 scan (planar and SPECT) double dose with delayed images as an alternative if PET not available
- Uric acid
- Discussion of fertility issues and sperm banking
- SPEP

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FOLL-1
**Follicular Lymphoma (grades 1-2)**

### STAGE

**Stage I, II**

- Locoregional RT\(^h\) or Chemotherapy followed by RT (category 2B)\(^i\) or Extended-field RT\(^i\) (category 2B) or Observation (selected cases)\(^j\)

**Indications for treatment:**
- Candidate for clinical trial\(^k\)
- Symptoms
- Threatened end-organ function
- Cytopenia secondary to lymphoma
- Bulky disease
- Steady progression
- Patient preference

**Complete response**\(^m\) or partial response\(^m\) → Follow-up every 3 mo for 1 y, then every 3-6 mo\(^n\) → Progressive disease\(^m,q\)

(For transformation See FOLL-4)

**Progressive disease**\(^m,q\) (For transformation See FOLL-4)

**No response**

**Indication present** → Local RT (palliation of locally symptomatic disease)\(^p\) or See Suggested Regimens (FOLL-B) or Clinical trial\(^l\)

**Follow-up** every 3 mo for 1 y, then every 3-6 mo\(^n\) → Progressive disease\(^m,q\)

(For transformation See FOLL-4)

**Progressive disease**\(^m,q\) (For transformation See FOLL-4)

**No indication** → Observe → Follow-up every 3 mo for 1 y, then every 3-6 mo\(^n\)

---

\(^g\)When determining initial treatment, consider excluding profoundly myelotoxic regimens for patients who may be eligible for autologous transplant.

\(^h\)Treatment of the involved lymphoid region (24-36 Gy).

\(^i\)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.

\(^j\)Observation may be appropriate in circumstances where toxicity of involved-field RT (locoregional) outweighs potential clinical benefit.

\(^k\)See GELF criteria (FOLL-A).

\(^l\)Given incurability with conventional therapy, consider investigational therapy as first line of treatment.

\(^m\)See Response Criteria for Lymphoma (NHODG-A).

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INITIAL RESPONSE

Complete response or partial response → Follow-up every 3 mo for 1 y, then every 3-6 mo

Progressive disease → Indications for treatment:
- Candidate for clinical trial
- Symptoms
- Threatened end-organ function
- Cytopenia secondary to lymphoma
- Bulky disease
- Steady progression
- Patient preference

No response or progressive disease → No indication → Observe

ADDITIONAL THERAPY

Follow-up includes repeat diagnostic tests, including imaging (based on site of disease and clinical presentation) as clinically indicated (about every 6 mo).

Patients in remission may be eligible for clinical trials.

Progressive disease should be histologically documented to rule out transformation (preferentially, biopsy gallium-avid sites or FDG uptake on PET), especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, gallium uptake increases over baseline, 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. See Management of Transformation (FOLL-4).

Clinical trials may involve novel agents, regimens or transplantation. See GELF criteria (FOLL-A).

Follow-up includes repeat diagnostic tests, including imaging (based on site of disease and clinical presentation) as clinically indicated (about every 6 mo).

Patients in remission may be eligible for clinical trials.

Progressive disease should be histologically documented to rule out transformation (preferentially, biopsy gallium-avid sites or FDG uptake on PET), especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, gallium uptake increases over baseline, 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. See Management of Transformation (FOLL-4).

Clinical trials may involve novel agents, regimens or transplantation.

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.
HISTOLOGICAL TRANSFORMATION TO DIFFUSE LARGE B-CELL LYMPHOMA

<table>
<thead>
<tr>
<th>Clinical trial or Radioimmunotherapy or Chemotherapy ± rituximab or Involved-field RT or Best Supportive Care (See NCCN Palliative Care Guidelines)</th>
<th>Responsive disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider autologous or allogeneic stem cell transplant(^t)</td>
<td>Consider autologous or allogeneic stem cell transplant(^t) or Clinical trial or Observation(^o)</td>
</tr>
<tr>
<td>Complete response(^m)</td>
<td>Partial response(^m)</td>
</tr>
<tr>
<td>Consider autologous or allogeneic stem cell transplant(^t) or Clinical trial</td>
<td>Clinical trial or Radioimmunotherapy or Palliative or best supportive care</td>
</tr>
<tr>
<td>No response or progressive disease(^m)</td>
<td></td>
</tr>
</tbody>
</table>

\(^m\) See Response Criteria for Lymphoma (NHODG-A).
\(^o\) Patients in remission are eligible for clinical trials.
\(^s\) If locoregional transformation, consider adding RT.
\(^t\) Strongly recommend this treatment be given in the context of a clinical trial; nonmyeloblative approaches may also be considered.

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.
**FLIPI CRITERIA**

<table>
<thead>
<tr>
<th>Risk group according to FLIPI chart</th>
<th>Number of factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0-1</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
</tr>
<tr>
<td>High</td>
<td>≥ 3</td>
</tr>
</tbody>
</table>

**FLIPI CRITERIA**

- **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**: ≥ 5

**Mannikin used for counting the number of involved areas.**

---

- **GELF CRITERIA**
  - 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
  - Splenomegalgy
  - 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)

---

- **This provides useful prognostic information without guiding therapeutic decisions.**
- **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.
- **The map of nodal sites is different than the conventional Ann Arbor site map.**
- **The map of nodal sites is different than the conventional Ann Arbor site map.**

---

**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.
### Follicular Lymphoma

**SUGGESTED TREATMENT REGIMENS**

* (in alphabetical order)

<table>
<thead>
<tr>
<th>Chemotherapy/Immunotherapy - single and combination therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line Therapy</strong></td>
</tr>
<tr>
<td>- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab (category 1)</td>
</tr>
<tr>
<td>- CVP (cyclophosphamide, vincristine, prednisone) + rituximab (category 1 for CVP + R)</td>
</tr>
<tr>
<td>- Fludarabine + rituximab</td>
</tr>
<tr>
<td>- FND (fludarabine, mitoxantrone, dexamethasone) + rituximab</td>
</tr>
<tr>
<td>- Rituximab</td>
</tr>
<tr>
<td>- Radioimmunotherapy (category 2B) or CHOP + rituximab followed by radioimmunotherapy (category 2B) [It is strongly recommended this treatment be on a prospective clinical study.]</td>
</tr>
</tbody>
</table>

| **First-line Extended Dosing** |
| Rituximab maintenance [It is strongly recommended this treatment be on a prospective clinical study.] |

| **Second-line and Subsequent Therapy** |
| - Autologous transplant |
| - Allogeneic transplant, for highly selected patients |
| - Chemo-immunotherapy (as in first-line therapy) |
| - Radioimmunotherapy |

| **Second-line Extended Dosing** |
| Rituximab maintenance [It is strongly recommended this treatment be on a prospective clinical study.] |

---

**Chemotherapy/Immunotherapy - single and combination therapy**

<table>
<thead>
<tr>
<th><strong>First-line Therapy</strong></th>
</tr>
</thead>
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<tr>
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<td>- Fludarabine + rituximab</td>
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<tr>
<td>- FND (fludarabine, mitoxantrone, dexamethasone) + rituximab</td>
</tr>
<tr>
<td>- Rituximab</td>
</tr>
<tr>
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</tr>
</tbody>
</table>

**First-line Extended Dosing**

- Rituximab maintenance [It is strongly recommended this treatment be on a prospective clinical study.]

**Second-line and Subsequent Therapy**

- Autologous transplant
- Allogeneic transplant, for highly selected patients
- Chemo-immunotherapy (as in first-line therapy)
- Radioimmunotherapy

**Second-line Extended Dosing**

- Rituximab maintenance [It is strongly recommended this treatment be on a prospective clinical study.]

---

### Notes:

- **Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
- **Selection of patients:** Requires adequate marrow cellularity > 15% and less than < 25% involvement of lymphoma in bone marrow, and platelets > 100,000. In patients with prior autologous stem cell transplant, referral to a tertiary care center is highly recommended for radioimmunotherapy.
- **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.
- **High dose therapy/autologous stem cell transplant:** Is an appropriate consolidative therapy to patients in second or third remission although the benefit is palliative.
- **In highly selected patients:** Trials of fully ablative and nonmyeloablative allogeneic stem cell transplant have shown long term survival advantage, although there is a treatment-related mortality rate of 25%.
- **In a previously rituximab naive patient:** Consolidation with rituximab can be considered.

---

**FOLL-B 2 of 2**
SUGGESTED TREATMENT REGIMENS

References

**Cyclophosphamide**

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


**CVP (cyclophosphamide, vincristine, prednisone) + rituximab**

**FND (fludarabine, mitoxantrone, dexamethasone) + rituximab**

**Radioimmunotherapy (first-line)**


**Radioimmunotherapy (second-line)**


**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.
**Gastric MALT Lymphoma**

**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 alone is not desirable for the initial diagnosis of lymphoma. In certain circumstances a combination of morphologic and flow cytometric studies may provide adequate information to provide a diagnosis.
- Adequate immunophenotyping to establish diagnosis\(^b\)
  - Paraffin panel: CD20 (L26/Pan B), CD3, CD5, CD10, bcl-2, kappa/lambda, CD 21 or CD23, cyclin D1 or
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10
- Helicobacter Pylori stain (gastric)

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Immunohistochemical studies
  - Frozen Section Panel: kappa/lambda, CD20
  - Paraffin panel: bcl-6, cyclin D1 (CD5+), CD43,\(^c\)
- Molecular genetic analysis to detect antigen receptor gene rearrangements; RT PCR for t(11;18)
- Cytogenetics or FISH for t(11;18),\(^d\) \([t(11;14), t(14;18)], 13q del\)

---

**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.

---

\(^a\)Nondiagnostic atypical lymphoid infiltrates that are H. Pylori positive, should be rebiopsied to confirm or exclude lymphoma prior to treatment of H. Pylori.

\(^b\)Typical immunophenotype: CD10-, CD5-, CD20+, CD23-/+, CD43-/+ and cyclin D1-, bcl-2 follicles-.

\(^c\)May be helpful to distinguish between benign and malignant B-cells in paraffin.

\(^d\)Disseminated disease is more likely in patients with extranodal gastric lymphoma with t(11;18) and in nongastric nodal lymphoma with trisomy 18.

---

**WORKUP**

**ESSENTIAL:**
- Physical exam with performance status
  - CBC, differential, platelets
  - Comprehensive metabolic panel
  - LDH
  - Additional H. pylori testing
  - Hepatitis B testing
  - Regional imaging appropriate to site of disease

**USEFUL IN SELECTED CASES**
- Endoscopic ultrasound
- Bone marrow biopsy ± aspirate
- Endoscopy with multiple biopsies of anatomical sites
- PET scan

---

See Initial Therapy (MALT-2)
### Gastric MALT Lymphoma

#### STAGE

<table>
<thead>
<tr>
<th>Stage</th>
<th>INITIAL THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IE, H. pylori positive</td>
<td>Currently accepted antibiotic therapy for H. pylori[^f]</td>
</tr>
<tr>
<td>Stage IE or II H. pylori negative</td>
<td>Consider antibiotic therapy for H. pylori as above or RT (30-33 Gy)[^g] (preferred) or Rituximab (if RT is contraindicated)</td>
</tr>
</tbody>
</table>

#### Stage III/IV (advanced-stage disease uncommon)

- **Indications for treatment:**
  - Candidate for clinical trial[^h]
  - Symptoms
  - GI bleeding
  - Threatened end-organ function
  - Bulky disease
  - Steady progression
  - Patient preference

- **Induction chemotherapy:**
  - Combination or single agent

- **Locoregional RT in specific settings**

- **Endoscopy for restaging, if evidence of recurrence:** manage per follicular lymphoma (see FOLL-3)[^i]

---

[^e]: See Staging of gastric MALT Lymphoma ([MALT-A](#)).

[^f]: A t(11;18) is a predictor for no response to antibiotics, alternate treatment should be considered.

[^g]: If negative by both histology and serum antibodies, RT recommended.

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

[^i]: Surgical resection is generally limited to specific clinical situations, ie, life-threatening hemorrhage.

[^See Suggested Treatment Regimens (FOLL-B)]:

---

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.
3-MONTH RESTAGING AND FOLLOW-UP ENDOSCOPY

H. pylori negative, Lymphoma negative
- Observe

H. pylori negative, Lymphoma positive
- Asymptomatic
  - Observe for another 3 mo
  - or Locoregional RT
- Symptomatic
  - RT

H. pylori positive, Lymphoma negative
- Stable disease
  - Second-line antibiotic treatment
- Progressive disease
  - RT

H. pylori positive, Lymphoma positive
- Restage at 3 mo with endoscopy/biopsy for H. pylori/lymphoma (restage earlier than 3 mo if symptomatic)

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**Gastric MALT Lymphoma**

### 6-MONTH RESTAGING AND FOLLOW-UP ENDOSCOPY

- **H. pylori negative**
  - **Lymphoma negative**
    - Restage at 6 mo with endoscopy and biopsy
  - **Lymphoma positive**
    - Consider other antibiotic treatment
- **H. pylori positive**
  - **Lymphoma negative**
    - Locoregional RT, if not previously treated or if prior XRT, see FOLL-2
  - **Lymphoma positive**
    - H. pylori positive
      - Locoregional RT, if not previously treated or if prior XRT, see FOLL-2

**FOLLOW-UP ENDOSCOPY**

- **Complete response**
  - Follow-up every 3 mo for 1 y, then every 3-6 mo
- **No response**
  - Repeat Endoscopy
  - Previous RT
    - Recurrence post RT
    - See follicular lymphoma indications for treatment (FOLL-3)
  - Previous antibiotic treatment
    - Recurrence post antibiotics
    - See follicular lymphoma indications for treatment (FOLL-3)
  - Locoregional RT

**Note:**

- Biopsy to rule out large cell lymphoma.
- Optimal interval for follow-up endoscopy is not known.
- Follow-up includes repeat diagnostic tests, including imaging (based on site of disease and clinical presentation) as clinically indicated (about every 6 mo).

---

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
## STAGING OF GASTRIC MALT LYMPHOMA: COMPARISON OF DIFFERENT SYSTEMS

<table>
<thead>
<tr>
<th>Lugano Staging System for gastrointestinal lymphomas</th>
<th>TNM Staging System adapted for gastric lymphoma</th>
<th>Ann Arbor stage</th>
<th>Tumor extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I Confined to GI tract (single primary or multiple, noncontiguous)</td>
<td>T1 N0 M0</td>
<td>I_E</td>
<td>Mucosa, submucosa</td>
</tr>
<tr>
<td></td>
<td>T2 N0 M0</td>
<td>I_E</td>
<td>Muscularis propria</td>
</tr>
<tr>
<td></td>
<td>T3 N0 M0</td>
<td>I_E</td>
<td>Serosa</td>
</tr>
<tr>
<td>Stage II Extending into abdomen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II_1 = local nodal involvement</td>
<td>T1-3 N1 M0</td>
<td>II_E</td>
<td>Perigastric lymph nodes</td>
</tr>
<tr>
<td>II_2 = distant nodal involvement</td>
<td>T1-3 N2 M0</td>
<td>II_E</td>
<td>More distant regional lymph nodes</td>
</tr>
<tr>
<td>Stage II_E Penetration of serosa to involve adjacent organs or tissues</td>
<td>T4 N0 M0</td>
<td>I_E</td>
<td>Invasion of adjacent structures</td>
</tr>
<tr>
<td>Stage IV Disseminated extranodal involvement or concomitant supradiaphragmatic nodal involvement</td>
<td>T1-4 N3 M0</td>
<td>III_E</td>
<td>Lymph nodes on both sides of the diaphragm/distant metastases (eg, bone marrow or additional extranodal sites)</td>
</tr>
<tr>
<td></td>
<td>T1-4 N0-3 M1</td>
<td>IV_E</td>
<td></td>
</tr>
</tbody>
</table>


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.
**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 alone is not desirable for the initial diagnosis of lymphoma. In certain circumstances a combination of morphologic and flow cytometric studies may provide adequate information to provide a diagnosis.
- Adequate immunophenotyping to establish diagnosis\(^b\)
  - Paraffin panel: CD20 (L26/Pan B), CD3, CD5, CD10, bcl-2, kappa lambda, CD 21 or CD23, cyclin D1 or
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10
- Helicobacter Pylori stain (gastric)

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Immunohistochemical studies
  - Frozen Section Panel: kappa/lambda, CD20
  - Paraffin panel: bcl-6, cyclin D1 (CD5+), CD43,\(^c\)
- Molecular genetic analysis to detect antigen receptor gene rearrangements; RT PCR for t(11;18)
- Cytogenetics or FISH for t(11;18),\(^d\) t(11;14), t(14;18), 13q del

**WORKUP**

**ESSENTIAL:**
- Physical exam with performance status
- CBC, differential, platelets
- Comprehensive metabolic panel
- LDH
- Regional imaging appropriate to site of disease

**USEFUL IN SELECTED CASES**
- Bone marrow biopsy ± aspirate
- Endoscopy with multiple biopsies of anatomical sites

\(^a\)Nondiagnostic atypical lymphoid infiltrates that are H. Pylori positive, should be rebiopsied to confirm or exclude lymphoma prior to treatment of H. Pylori.

\(^b\)Typical immunophenotype: CD10–, CD5–, CD20+, CD23–/+, CD43–/+ and cyclin D1–, bcl-2 follicles–.

\(^c\)May be helpful to distinguish between benign and malignant B-cells in paraffin.

\(^d\)Disseminated disease is more likely in patients with extranodal gastric lymphoma with t(11;18) and in nongastric nodal lymphoma with trisomy 18.

**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.
Nongastric MALT Lymphoma

**STAGE**

**TREATMENT**

<table>
<thead>
<tr>
<th>Stage IE-II</th>
<th>Locoregional RT (20-30 Gy)</th>
<th>RT may be considered for completely resected, negative margins</th>
<th>Follow-up every 3 mo for 1 y, then every 3-6 mo for 3 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extranodal (multiple sites)</td>
<td>Local recurrence</td>
<td>Manage per NCCN Follicular Lymphoma Guidelines for advanced stage (FOLL-3)</td>
<td></td>
</tr>
<tr>
<td>Stage III, IV: extranodal disease and multiple nodal sites</td>
<td>Manage per Follicular Lymphoma Guidelines for advanced stage (FOLL-3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IE-IV, MALT lymphomas coexistent with large cell lymphoma</td>
<td>Treat per NCCN Diffuse Large B-Cell Lymphoma Guidelines (BCEL-1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

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

Treatment of each site may be indicated (e.g., bilateral conjunctiva).
DLBCL coexistent with MALT cell lymphoma is managed as DLBCL.
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.
Dose is site dependent with lower dose reserved for eye involvement.
Follow-up includes repeat diagnostic tests, including imaging (based on site of disease and clinical presentation) as clinically indicated (about every 6 mo).

RT or Manage per NCCN Follicular Lymphoma Guidelines for advanced stage (FOLL-3)
### Nodal Marginal Zone Lymphoma

#### DIAGNOSIS

**ESSENTIAL:**
- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.¹
- An FNA alone is not desirable for the initial diagnosis of lymphoma. In certain circumstances a combination of morphologic and flow cytometric studies may provide adequate information to provide a diagnosis.
- Adequate immunophenotyping to establish diagnosis²
  - Paraffin panel: CD20 (L26/Pan B), CD3, CD5, CD10, bcl-2, kappa/lambda, CD21 or CD23, cyclin D1
  - or
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10
- Helicobacter Pylori stain (gastric)

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Immunohistochemical studies
  - Frozen Section Panel: kappa/lambda, CD20
  - Paraffin panel: bcl-6, cyclin D1 (CD5+), CD43,³
- Molecular genetic analysis to detect antigen receptor gene rearrangements; RT PCR for t(11;18)
- Cytogenetics or FISH for t(11;18), [t(11;14), t(14;18)], 13q del

### WORKUP

**ESSENTIAL:**
- Physical exam with performance status
- CBC, differential, platelets
- Comprehensive metabolic panel
- LDH
- Hepatitis B testing
- Regional imaging appropriate to site of disease
- Evaluation to rule out extranodal primary nodes
  - Neck nodes: ocular, thyroid and salivary gland
  - Axillary nodes: lung, salivary gland and skin
  - Mediastinal/hilar nodes: lung
  - Abdominal nodes: splenic and GI
  - Inguinal/iliac nodes: GU and skin

**USEFUL IN SELECTED CASES**
- Bone marrow biopsy ± aspirate

---

¹Nondiagnostic atypical lymphoid infiltrates that are H. Pylori positive, should be rebiopsied to confirm or exclude lymphoma prior to treatment of H. Pylori.

²Typical immunophenotype: CD10-, CD5-, CD20+, CD23-/+, CD43-/+ and cyclin D1-, bcl-2 follicles-.

³May be helpful to distinguish between benign and malignant B-cells in paraffin.

⁴Disseminated disease is more likely in patients with extranodal gastric lymphoma with t(11;18) and in nongastric nodal lymphoma with trisomy 18.

---

**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.
**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 alone is not desirable for the initial diagnosis of lymphoma. In certain circumstances a combination of morphologic and flow cytometric studies may provide adequate information to provide a diagnosis.
- Adequate immunophenotyping to establish diagnosis\(^b\)
  - Paraffin panel: CD20 (L26/Pan B), CD3, CD5, CD10, bcl-2, kappa/lambda, CD21 or CD23, cyclin D1 or
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10
- Helicobacter Pylori stain (gastric)

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Immunohistochemical studies
  - Frozen Section Panel: kappa/lambda, CD20
  - Paraffin panel: bcl-2, cyclin D1 (CD5+), CD43\(^c\)
- Molecular genetic analysis to detect antigen receptor gene rearrangements; RT PCR for t(11;18)
- Cytogenetics orFISH for t(11;18),\(^d\) [t(11;14), t(14;18)], 13q del

\(^a\)Nondiagnostic atypical lymphoid infiltrates that are H. Pylori positive, should be rebiopsied to confirm or exclude lymphoma prior to treatment of H. Pylori.

\(^b\)Typical immunophenotype: CD10-, CD5-, CD20+, CD23-/+, CD43-/+ and cyclin D1-, bcl-2 follicles-.

\(^c\)May be helpful to distinguish between benign and malignant B-cells in paraffin.

\(^d\)Disseminated disease is more likely in patients with extranodal gastric lymphoma with t(11;18) and in nongastric nodal lymphoma with trisomy 18.

**WORKUP**

**ESSENTIAL:**
- Physical exam with performance status
- CBC, differential, platelets
- Comprehensive metabolic panel
- LDH
- Hepatitis B and C testing
- Regional imaging appropriate to site of disease
- Bone marrow biopsy ± aspirate

See Initial Therapy (SPLN-2)

---

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

Splenic Marginal Zone Lymphoma

**Splenomegaly**

- **Hepatitis C positive**
  - GI evaluation
  - **Indications for treatment of hepatitis**
  - **Appropriate treatment**
  - **Follow-up every 3 mo for 1 y, then every 3-6 mo**

- **Hepatitis C negative**
  - Observation
  - **No symptoms**
  - **No indications for treatment of hepatitis**
  - **Cytopenias**
  - **Symptoms**
  - **Splenectomy** (preferred)
  - **or Rituximab** (optional)

**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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Mantle Cell Lymphoma

**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 alone is not desirable for the initial diagnosis of lymphoma. However, in certain circumstances a combination of morphologic and flow cytometric studies may provide adequate information to provide a diagnosis.
- Adequate immunophenotyping to establish diagnosis.
  - Paraffin panel: CD20 (L26/Pan B), CD3, CD5, cyclin D1
  - or
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10, FMC7, and
  - FISH for t(11;14)

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Frozen section panel: kappa/lambda, CD5, CD23, CD10, CD43, CD79a
- Paraffin panel: CD43, p53
- Molecular genetic analysis to detect antigen receptor gene rearrangements; bcl-1 rearrangements
- Cytogenetics or FISH for t(11;14)

---

**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
- Chest x-ray, PA and LAT and/or chest CT
- Bone marrow biopsy ± aspirate
- Abdominal/pelvic CT
- Colonoscopy
- Hepatitis B testing

**USEFUL UNDER CERTAIN CIRCUMSTANCES**
- Upper endoscopy
- Neck CT
- Uric acid
- Discussion of fertility issues and sperm banking
- Lumbar puncture (for blastic variant or CNS symptoms)
- Beta-2-microglobulin

---

**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.
Mantle Cell Lymphoma

**INDUCTION THERAPY**

- **Stage I, II (localized presentation, extremely rare)**
  - Clinical trial or See Suggested Regimens *(MANT-A)* or RT (30-36 Gy)\(^e\)

- **Stage III, IV**
  - Clinical trial or See Suggested Regimens *(MANT-A)* or Observation only in highly selected cases\(^f\)

**INITIAL RESPONSE**

- Complete response\(^g,h\) → Relapse
- Partial response\(^g,h\)
- Progression\(^h\)

**RELAPSE**

- Clinical trial\(^g\) or Second-line treatment with palliative intent
  - XRT
  - See Suggested Regimens *(MANT-A)*

---


\(^f\) Patients who are asymptomatic with stable adenopathy and nonbulky disease, usually have a nodular pattern.

\(^g\) Option for clinical trials of adjuvant therapy or for relapsed disease involving high-dose therapy with autologous or allogeneic stem cell transplant, immunotherapy with nonmyeloablative stem cell transplant, or evaluation of treatment with new agents are appropriate.

\(^h\) See Response Criteria for Lymphoma *(NHODG-A)*.

---

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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
SUGGESTED TREATMENT REGIMENS\textsuperscript{a}
(in alphabetical order)

<table>
<thead>
<tr>
<th>First-line Therapy\textsuperscript{b,c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Rituximab + CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) in selected older patients who cannot tolerate more intensive therapy</td>
</tr>
<tr>
<td>• Rituximab + HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with methotrexate and cytarabine</td>
</tr>
<tr>
<td>• Rituximab + EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>First-line Consolidation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Allogeneic transplant in the context of a clinical trial (nonmyeloablative or myeloablative)</td>
</tr>
<tr>
<td>• ASCT\textsuperscript{d} (category 2B)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Second-line Therapy\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bortezomib</td>
</tr>
<tr>
<td>• Cladribine</td>
</tr>
<tr>
<td>• FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab) ± rituximab maintenance</td>
</tr>
<tr>
<td>• FMR (fludarabine, mitoxantrone, rituximab)</td>
</tr>
<tr>
<td>• FC (fludarabine, cyclophosphamide) ± rituximab</td>
</tr>
<tr>
<td>• PCR (pentostatin, cyclophosphamide, rituximab)</td>
</tr>
<tr>
<td>• Thalidomide + rituximab</td>
</tr>
</tbody>
</table>

\textsuperscript{a}See references for regimens MANT-A 2 of 2.
\textsuperscript{b}For regimens including anthracycline or anthracenediones, appropriate cardiac evaluation (MUGA or ECHO) should be undertaken.
\textsuperscript{c}There are no prospective randomized comparative trials with induction therapy regimens for mantle cell lymphoma.
\textsuperscript{d}Randomized data with anthracycline-containing regimens suggest an improvement in progression free survival with the addition of first-line autologous stem cell consolidation. Overall survival benefit has not been demonstrated.

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

First-line Therapy
Rituximab + HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with methotrexate and cytarabine
Rituximab + CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab

ASCT (first-line consolidation) (category 2B)

Second-line Therapy
FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab) ± rituximab maintenance
Thalidomide + rituximab

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.
**Diffuse Large B-Cell Lymphoma**

**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 alone is not desirable for the initial diagnosis of lymphoma. However, in certain circumstances a combination of morphologic and flow cytometric studies may provide adequate information to provide a diagnosis.
- Adequate immunophenotyping to establish diagnosis:
  - Paraffin panel: CD20 (L26/Pan B), CD3, CD10, bcl-6, bcl-2 protein, MIB1(Ki-67), CD5
  - 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:
  - Frozen section: CD19, CD20, CD23, CD5, kappa/lambda, CD10
  - Paraffin panel: cyclin D1, CD43, kappa/lambda, MUM1
- Molecular genetic analysis to detect antigen receptor gene rearrangements; bcl-2, bcl-1, c-myc rearrangements
- Cytogenetics or FISH

**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 x-ray, PA and LAT
- Chest/abdominal/pelvic CT
- Unilateral or bilateral bone marrow biopsy (1-2 cm) ± aspirate
- Calculation of International Prognostic Index (IPI)
- Determination of ejection fraction: MUGA scan or echocardiogram
- Beta-2-microglobulin (category 2B)
- Hepatitis B testing

**USEFUL IN SELECTED CASES:**
- PET scan (preferred) or Gallium-67 scan (planar and SPECT) double dose with delayed images as an alternative if PET not available
- Neck CT
- Head CT or MRI
- Discussion of fertility issues and sperm banking
- HIV
- Lumbar puncture, if paranasal sinus, testicular, parameningeal, peri-orbital, CNS, paravertebral, bone marrow with large cell lymphoma or HIV 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.

---

**a** DLBCL coexistent with follicular lymphoma of any grade, DLBCL coexistent with gastric MALT lymphoma, DLBCL coexistent with nongastric MALT lymphoma, anaplastic large-cell, and peripheral T-cell lymphomas are also treated according to this guideline. Rituximab should not be included in the treatment of T-cell lymphoma. This pathway is commonly used to treat Follicular Lymphoma grade 3. Cutaneous B-Cell is not included.

**b** Typical immunophenotype: CD20+, CD45+, CD3-.

**c** May be helpful to distinguish between benign and malignant B-cells in paraffin.

**d** See International Prognostic Index (BCEL-A).
**Diffuse Large B-Cell Lymphoma**

**INDUCTION THERAPY**

<table>
<thead>
<tr>
<th>STAGE</th>
<th>INDUCTION THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I, II&lt;sup&gt;e,f&lt;/sup&gt;</td>
<td>RCHOP 6-8 cycles ± locoregional RT (30-36 Gy to involved-lymphoid region) (category 2B for RT) or RCHOP x 3 cycles + locoregional RT (30-36 Gy)</td>
</tr>
<tr>
<td>Bulky (≥ 10 cm)</td>
<td>RCHOP 6-8 cycles + locoregional RT (30-40 Gy to involved lymphoid region) (category 1)</td>
</tr>
<tr>
<td>Stage III, IV&lt;sup&gt;e,g&lt;/sup&gt; + age-adjusted (aa) IPI&lt;sup&gt;d&lt;/sup&gt;</td>
<td>RCHOP 6-8 cycles&lt;sup&gt;i,j&lt;/sup&gt; (category 1)&lt;sup&gt;k&lt;/sup&gt;</td>
</tr>
<tr>
<td>Low/Low-intermediate risk (aaIPI 0-1)</td>
<td>Clinical trial&lt;sup&gt;i&lt;/sup&gt; (preferred) or RCHOP 6-8 cycles&lt;sup&gt;i,j&lt;/sup&gt; (category 1)&lt;sup&gt;k&lt;/sup&gt;</td>
</tr>
<tr>
<td>High-intermediate/high risk (aaIPI ≥ 2)</td>
<td></td>
</tr>
</tbody>
</table>

**Adverse risk factors present:**
- Elevated LDH
- Stage II
- Age > 60 y
- Performance status ≥ 2

**Adverse risk factors not present**

**Consider prophylaxis for tumor lysis syndrome**

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<sup>d</sup>See International Prognostic Index (BCEL-A).
<sup>e</sup>In testicular lymphoma, after completion of chemotherapy, RT should be given to contralateral testis (30-36 Gy).
<sup>f</sup>In patients who are not candidates for chemotherapy involved field radiation therapy (IFRT) is recommended.
<sup>g</sup>In selective settings (testicular, paranasal sinus, epidural, bone marrow involvement) CNS prophylaxis should be given (4-8 doses of intrathecal methotrexate and/or cytarabine during the course of treatment.)

---

<sup>h</sup>Recommendations are for HIV-negative lymphoma only.
<sup>i</sup>Based on current clinical trials, CHOP is preferable due to reduced toxicities, but other comparable anthracycline-based regimens are acceptable.
<sup>j</sup>For other regimens, see BCEL-B.
<sup>k</sup>In selected cases, RT to initially bulky sites of disease may be beneficial (category 2B).
<sup>l</sup>May include high-dose therapy.
**Pre RT Evaluation**

- **Complete response** or CRu (unconfirmed) → Complete planned course of treatment
- **Partial response** → Complete course of therapy with higher RT dose (40-45 Gy) or Autologous stem cell transplant or Clinical trial (may include allogeneic stem cell transplant)
- **No response or progressive disease** → See Additional Therapy for Relapse (BCEL-5) or RT in select patients who are not candidates for chemotherapy

**Follow-Up Therapy**

- **At completion of treatment, repeat all positive studies.** If PET positive, strongly recommend rebiopsy prior to proceeding to additional therapy.

**End of Treatment Restaging**

Follow-up every 3 mo for 24 mo, then every 6 mo for 36 mo

- **Complete response** → No response or progressive disease
- **Partial response** → Follow-up

**Initial Response**

- Follow-up every 3 mo for 24 mo, then every 6 mo for 36 mo

**Relapse,** See Additional Therapy (BCEL-5)

---

\(m\) PET or Gallium scans should be used to assess residual abnormalities on CT scans, especially if done pre-treatment.

\(n\) See Response Criteria for Lymphoma (NHODG-A).

\(o\) Documented PR includes a biological measure of disease: positive gallium scan, positive PET scan, or ideally positive biopsy.

\(p\) Patients in first remission may be candidates for consolidation trials including autologous transplant.

---

**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.
**Diffuse Large B-Cell Lymphoma**

**INTERIM RESTAGING**

- **Stage III, IV:**
  - After 3-4 cycles, repeat all positive studies
  - Rebiopsy in certain circumstances

**Follow-up Therapy**

- Complete response or CR (unconfirmed) → Continue RCHOP to a total of 6-8 cycles
- Partial response → Continue RCHOP to a total of 6-8 cycles or Clinical trial
- No response or progressive disease → See Additional Therapy for Relapse (BCEL-5) or RT in select patients who are not candidates for chemotherapy

**End of Treatment Restaging**

- At completion of treatment, repeat all positive studies. If PET positive, strongly recommend rebiopsy prior to proceeding to additional therapy.

**Initial Response**

- Follow-up every 3 mo for 24 mo, then every 6 mo for 36 mo
- Partial response
- No response or progressive disease

**Relapse,**

- See Additional Therapy (BCEL-5)

---

**Notes:**

- 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.

---

*See Response Criteria for Lymphoma (NHODG-A).*

*Documented PR includes a biological measure of disease: positive gallium scan, positive PET scan, or ideally positive biopsy.*

*Patients in first remission may be candidates for consolidation trials including autologous transplant.*

---

*PET or Gallium scans should be used to assess residual abnormalities on CT scans, especially if done pre-treatment.*

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Relapse/refractory disease

Candidate for high-dose therapy

See Suggested Regimens (BCEL-B)

Complete response or partial response

Non candidate for high-dose therapy

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

No response

Response #2

Candidate for high-dose therapy

Autologous stem cell transplant (category 1 for CR, category 2A for all others) \pm involved field RT q

Clinical trial or Clinical trial (including the option of allogeneic stem cell transplant)

Consolidation/additional therapy

Consolidation/additional therapy

Relapse #2 or greater

Clinical trial or Individual approach

Clinical trial or Best supportive care

Additional RT can be given before or after stem cell transplant to sites of bulky disease.

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.

See Response Criteria for Lymphoma (NHODG-A).

\( q \) Additional RT can be given before or after stem cell transplant to sites of bulky disease.

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

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

<table>
<thead>
<tr>
<th>ALL PATIENTS:</th>
<th>INTERNATIONAL INDEX, ALL PATIENTS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60 years</td>
<td>Low</td>
</tr>
<tr>
<td>Serum LDH &gt; 1 x normal</td>
<td>Low intermediate</td>
</tr>
<tr>
<td>Performance status 2-4</td>
<td>High intermediate</td>
</tr>
<tr>
<td>Stage III or IV</td>
<td>High</td>
</tr>
<tr>
<td>Extranodal involvement &gt; 1 site</td>
<td>High</td>
</tr>
</tbody>
</table>

## AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX\(^a\)

<table>
<thead>
<tr>
<th>PATIENTS ≤ 60 YEARS:</th>
<th>INTERNATIONAL INDEX, PATIENTS ≤ 60 YEARS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage III or IV</td>
<td>Low</td>
</tr>
<tr>
<td>Serum LDH &gt; 1 x normal</td>
<td>Low/intermediate</td>
</tr>
<tr>
<td>Performance status 2-4</td>
<td>High/intermediate</td>
</tr>
<tr>
<td></td>
<td>High</td>
</tr>
</tbody>
</table>

SUGGESTED TREATMENT REGIMENS\textsuperscript{a}  
(in alphabetical order)

**First-line Therapy\textsuperscript{b}**
- Rituximab + CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)
- Dose dense RCHOP 14 (category 3)
- Rituximab + EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) (category 2B)

**Second-line Therapy\textsuperscript{b}**
- DHAP (dexamethasone, cisplatin, cytarabine) ± R
- ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± R
- GDP (gemcitabine, dexamethasone, cisplatin) ± R
- ICE (ifosfamide, carboplatin, etoposide) ± R
- miniBEAM (carmustine, etoposide, cytarabine, melphalan) ± R
- MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± R

\textsuperscript{a}See references for regimens BCEL-B 2 of 2.

\textsuperscript{b}For regimens including anthracycline or anthracenediones, appropriate cardiac evaluation (MUGA or ECHO) should be undertaken.
SUGGESTED TREATMENT REGIMENS

References

First-line Therapy
Rituximab + CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)

Second-line Therapy
GDP (gemcitabine, dexamethasone, cisplatin) ± R
**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 alone is not desirable for the initial diagnosis of lymphoma. However, in certain circumstances a combination of morphologic and flow cytometric studies may provide adequate information to provide a diagnosis.
- Adequate immunophenotyping to establish diagnosis
  - Paraffin panel: CD45 (LCA), CD20 (L26/Pan B), CD3, CD10, MIB1(Ki-67), bcl-2, bcl-6, TdT or
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD20, CD3, CD5, CD19, CD10, TdT
- Cytogenetics/FISH

**Useful Under Certain Circumstances:**
- Additional immunohistochemical studies to establish lymphoma subtype
  - Frozen: kappa/lambda
  - Paraffin panel: TdT, kappa/lambda, ISH for EBER
- Molecular genetic analysis to detect antigen receptor gene rearrangements; c-myc rearrangement
- Cytogenetics or FISH for t(8;14) or variants, c-myc, IgH, bcl-2, bcl-6 rearrangements

---

**Workup**

**Essential:**
- Physical exam: attention to node-bearing areas, including Waldeyer’s ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC, differential, platelets
- LDH
- Comprehensive metabolic panel
- Uric acid
- Chest x-ray, PA and LAT or chest CT
- Chest/abdominal/pelvic CT
- Lumbar puncture
- Unilateral or bilateral bone marrow biopsy ± aspirate
- HIV (category 2B)
- Hepatitis B testing

**Useful in Selected Cases:**
- Neck CT
- Discussion of fertility issues and sperm banking
- Beta-2-microglobulin

---

**Notes:**

- WHO classification considers classic Burkitt’s lymphoma and Burkitt’s-like lymphoma a single entity.
- Typical immunophenotype: slg+, CD10+, CD20+, TdT-, Ki67+ (100%), bcl-2-, bcl-6+, cMYCR only by cytogenetics or FISH.

---

**See Risk Assessment and Induction Therapy (BURK-2)**
**Burkitt’s Lymphoma**

### Risk Assessment
- **Low risk**
  - Normal LDH
  - Completely resected abdominal lesion or single extra-abdominal mass
  - Clinical trial or See Suggested Regimens (BURK-A)

- **High risk**
  - Clinical trial or See Suggested Regimens (BURK-A)

### Induction Therapy
- **Low risk**
  - Clinical trial or See Suggested Regimens (BURK-A)
  - Complete response → Follow-up after complete response: every 2 mo for 1 y, then every 3 mo for 1 y, then every 6 mo

- **High risk**
  - Clinical trial or See Suggested Regimens (BURK-A)
  - Complete response → Follow-up after complete response: every 2 mo for 1 y, then every 3 mo for 1 y, then every 6 mo

### Initial Response
- Complete response → Follow-up after complete response: every 2 mo for 1 y, then every 3 mo for 1 y, then every 6 mo

### Relapse
- Complete response → Follow-up after complete response: every 2 mo for 1 y, then every 3 mo for 1 y, then every 6 mo
- < Complete response → Consolidation or Clinical trial

### Clinical Trials
- NCCN recommends clinical trials for the best management of Burkitt's Lymphoma patients.
- Relapse after 2 y is rare, therefore, follow-up should be individualized according to patient characteristics.

---

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

---

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
SUGGESTED TREATMENT REGIMENS\textsuperscript{a}
(in alphabetical order)

\begin{tabular}{|l|}
\hline
\textbf{Low Risk- Combination Regimens}\textsuperscript{b}  \\
\hline
\hspace{1cm}• CODOX-M: cyclophosphamide, vincristine,  \\
\hspace{1cm}doxorubicin, high-dose methotrexate \pm rituximab  \\
\hspace{1cm}(regimen includes intrathecal methotrexate)  \\
\hspace{1cm}• HyperCVAD (cyclophosphamide, vincristine,  \\
\hspace{1cm}doxorubicin, dexamethasone) alternating with  \\
\hspace{1cm}methotrexate + cytarabine, \pm rituximab  \\
\hspace{1cm}(regimen includes intrathecal methotrexate)  \\
\hline
\textbf{High Risk- Combination Regimens}\textsuperscript{b}  \\
\hline
\hspace{1cm}• CODOX-M/IVAC: cyclophosphamide, vincristine,  \\
\hspace{1cm}doxorubicin, high-dose methotrexate + ifosfamide,  \\
\hspace{1cm}etoposide, high-dose cytarabine, \pm rituximab  \\
\hspace{1cm}(regimen includes intrathecal methotrexate)  \\
\hspace{1cm}• HyperCVAD (cyclophosphamide, vincristine,  \\
\hspace{1cm}doxorubicin, dexamethasone) + methotrexate +  \\
\hspace{1cm}cytarabine \pm rituximab  \\
\hspace{1cm}(regimen includes intrathecal methotrexate)  \\
\hline
\end{tabular}

Consider SCT for patients in relapse  

CHOP is not adequate therapy.

\textsuperscript{a}See references for regimens BURK-A 2 of 2.

\textsuperscript{b}For regimens including anthracycline or anthracenediones, appropriate cardiac evaluation (MUGA or ECHO) should be undertaken.

\textbf{Note:} All recommendations are category 2A unless otherwise indicated.  

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

References

**Low Risk- Combination Regimens**
CODOX-M: cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate ± rituximab (regimen includes intrathecal methotrexate)
HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with methotrexate + cytarabine, ± rituximab (regimen includes intrathecal methotrexate)

**High Risk- Combination Regimens**
CODOX-M/IVAC: cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate + ifosfamide, etoposide, high-dose cytarabine, ± rituximab (regimen includes intrathecal methotrexate)
HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) + methotrexate + cytarabine ± rituximab (regimen includes intrathecal methotrexate)

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.
**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 alone is not desirable for the initial diagnosis of lymphoma. However, in certain circumstances a combination of morphologic and flow cytometric studies may provide adequate information to provide a diagnosis.
- Adequate immunophenotyping to establish diagnosis
  - Paraffin panel: CD45 (LCA), CD20 (L26/Pan B), 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, CD14, CD13, CD33, CD1a, cytoplasmic CD3, CD22

**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 for c-myc, t(8;14) and variants, t(9;22)

**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 x-ray, PA and LAT or chest CT
- Abdominal/pelvic CT
- Lumbar puncture
- Bilateral or unilateral bone marrow biopsy ± aspirate with flow and cytogenetics
- Hepatitis B testing

**USEFUL IN SELECTED CASES:**
- Head MRI
- Discussion of fertility issues and sperm banking
- Beta-2-microglobulin

---

*aTypical immunophenotype:
LBL-B: sIg-, CD10+, CD19+, CD20-/-, TdT+.
LBL-T: sIg-, CD10-, CD19/20-, CD3-/+, CD4/8+/+, CD1a+/-, TdT+, CD2+, CD7+.*

---

**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.
Lymphoblastic Lymphoma

**CLINICAL ASSESSMENT**

Prophylaxis for tumor lysis syndrome is mandatory

**INDUCTION THERAPY**

Stage I–IV (disease is considered to be systemic) → Clinical trial\(^ b\) or See Suggested Regimens (BLAST-A)

**INITIAL RESPONSE**

- Complete response\(^ c\) → Observe or Clinical trial
- Partial response\(^ c\) → Clinical trial\(^ b\) or Best supportive care

**RELAPSE**

Relapse → Attempt reinduction with combination chemotherapy or Allogeneic HSCT or Clinical trial

---

\(^ b\) For poor risk patients, consideration of allogeneic or autologous transplant is appropriate.

\(^ c\) See Response Criteria for Lymphoma (NHODG-A).

**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
SUGGESTED TREATMENT REGIMENS\textsuperscript{a,b}
(in alphabetical order)

- CALGB ALL regimen
- Cytarabine + high-dose mitoxantrone, including intrathecal methotrexate
- High-dose cytarabine + rituximab or High-dose methotrexate + rituximab including intrathecal methotrexate
- HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with methotrexate + cytarabine, including intrathecal methotrexate
- Standard vincristine/prednisone induction followed by intensification, including intrathecal methotrexate

Maintenance chemotherapy - the use of maintenance is variable at NCCN institutions, some use up to 2 y of maintenance and other NCCN institutions do not use maintenance.

CNS prophylaxis to 24 Gy XRT should be considered (category 2B).

\textsuperscript{a}See references for regimens BLAST-A 2 of 2.
\textsuperscript{b}For regimens including anthracycline or anthracenediones, appropriate cardiac evaluation (MUGA or ECHO) should be undertaken.
SUGGESTED TREATMENT REGIMENS

References

CALGB ALL regimen

**Cytarabine + high-dose mitoxantrone, including intrathecal methotrexate**

**High-dose cytarabine + rituximab or High-dose methotrexate + rituximab including intrathecal methotrexate**
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 alone is not desirable for the initial diagnosis of lymphoma. However, in certain circumstances a combination of morphologic and flow cytometric studies may provide adequate information to provide a diagnosis.
- Adequate immunophenotyping to establish diagnosis
  - Paraffin panel: CD45 (LCA), CD20 (L26/Pan B), CD3, CD10, bcl-2, bcl-6, Ki-67, CD138, kappa/lambda, HTLV8
  or
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD3, CD5, CD19, CD10, TdT, CD14, CD20

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- Additional immunohistochemical studies to establish lymphoma subtype
  - DLBCL, Burkitt’s, Plasmablastic: CD10, bcl-2, Ki-67, bcl-6, CD138
- Molecular genetic analysis to detect antigen receptor gene rearrangements (bcl-2, bcl-6, c-myc)
- Cytogenetics or FISH (bcl-2, bcl-6, c-myc)
- Epstein-Barr virus (EBER) -ISH

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 x-ray, PA and LAT or chest CT
- Abdominal/pelvic CT
- Bone marrow biopsy ± aspirate
- CD4 count
- HIV
- LP
- Viral load
- Hepatitis B testing

USEFUL IN SELECTED CASES
- UGI/barium enema/endoscopy
- Neck CT
- Plain bone radiographs and bone scan
- Discussion of fertility issues and sperm banking
- Stool guaiac, if anemic
- Beta-2-microglobulin
- PET scan (preferred) or Gallium-67 scan (planar and SPECT) double dose with delayed images as an alternative if PET not available
- Brain MRI with gadolinium, or head CT

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.
AIDS-Related B-Cell Lymphomas

TREATMENT AND FOLLOW-UP

- Antiretrovirals
- **Manage as per Burkitt's Lymphoma (BURK-2):** CODOX-M/IVAC:
  - cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate + ifosfamide, etoposide, high-dose cytarabine
- Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
- CDE (cyclophosphamide, doxorubicin, etoposide)
- GCSF for all patients

**Primary CNS lymphoma**

- Consider high-dose methotrexate
- Consider radiotherapy alone
- Antiretrovirals

**Diffuse large B-cell lymphoma**

- Suggested regimens: Dose-adjusted EPOCH, CDE, CHOP
- Antiretrovirals
- GCSF for all patients
- Intrathecal therapy (IT) (category 2B)

**Burkitt's lymphoma**

- If patient is receiving effective anti-retroviral therapy, treat as [Burkitt's Lymphoma (see BURK-1)](#).
- Prophylactic IT methotrexate is used at some institutions for all patients. At other NCCN institutions, patients with HIV-associated DLBCL receive IT methotrexate in selective settings (testicular, paranasal sinus, epidural, bone marrow involvement).

**See Induction Therapy for Diffuse Large B-Cell Lymphoma (BCEL-1)**

- Consider CHOP or CHOP with high-dose methotrexate
- Avoid methotrexate dose > 3 g/m²
- GCSF for all patients
- Antiretrovirals

---

*a* If patient is receiving effective anti-retroviral therapy, treat as [Burkitt's Lymphoma (see BURK-1)](#).


*c* Prophylactic IT methotrexate is used at some institutions for all patients. At other NCCN institutions, patients with HIV-associated DLBCL receive IT methotrexate in selective settings (testicular, paranasal sinus, epidural, bone marrow involvement).

---

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**Peripheral T-Cell Lymphomas**

**excluding primary cutaneous T-cell lymphomas**

**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 alone is not sufficient for the initial diagnosis of peripheral T Cell lymphoma.
- Adequate immunophenotyping to establish diagnosis
  - Paraffin panel: CD20 (L26/Pan B), CD3, CD10, bcl-6, bcl-2 protein M1B1 (Ki-67), CD5, CD30, CD2, CD4, CD6, CD7, CD56, CD21, CD23, EBER, ALK-1
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD3, CD5, CD19, CD10, CD20, CD30, CD4, CD8, CD7, CD2
- Molecular genetic analysis to detect antigen receptor gene rearrangements and variants and t2;5 variants

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Additional immunohistochemical studies to establish lymphoma subtype
- Cytogenetics or FISH

**WORKUP**

**ESSENTIAL:**
- 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
- Calculation of International Prognostic Index (IPI)\(^b\)
- Determination of ejection fraction: MUGA scan or echocardiogram

**USEFUL IN SELECTED CASES:**
- PET scan
- Neck CT
- Head MRI
- Skin biopsy
- Liver biopsy
- Endoscopy
- Discussion of fertility issues and sperm banking
- HIV

---

\(^a\)Histologies included are peripheral T-cell lymphoma (PTCL) NOS, angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma (ALCL) noncutaneous, ALK-1 negative.

\(^b\)See International Prognostic Index (TCEL-A).

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Consider prophylaxis for tumor lysis syndrome

**Stage I, II**
- Clinical trial (preferred) or Aggressive chemotherapy\(^ c \) 6-8 cycles + locoregional RT (30-40 Gy to involved lymphoid region)
- Interim restaging: Repeat all prior positive studies Rebiopsy if PET positive
- See Follow-up Therapy (TCEL-3)

**Stage III, IV + age-adjusted IPI\(^ b \)**
- Clinical trial (preferred) or Aggressive chemotherapy\(^ c \) 6-8 cycles
- At completion of treatment, repeat all positive studies. If PET positive, consider rebiopsy.
- Partial response
- Complete response
  - ALCL ALK-1 positive
  - Observe
  - ALCL ALK-1 negative
  - PTCL NOS
  - AILT
  - Observe or Consider high dose therapy with stem cell rescue
- No response or progressive disease

**Relapse,**

See Additional Therapy (TCEL-4)

\( ^b \)See International Prognostic Index (TCEL-A).
\( ^c \)See Suggested Treatment Regimens (TCEL-B).

**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.
At completion of treatment, repeat all positivestudies. If PET positive, consider rebiopsy.

**INTERIM RESPONSE**

- **Complete response**
  - Complete planned course of treatment (RT)

- **Partial response**
  - RT (30-40 Gy) or Autologous stem cell transplant or Clinical trial (may include allogeneic stem cell transplant)

- **No response or progressive disease**
  - RT or See Additional Therapy for Relapse (TCEL-4)

**END OF TREATMENT RESTAGING**

- **Complete response**
  - Follow-up every 3 mo for 24 mo, then every 6 mo for 36 mo

- **Partial response**
  - See Additional Therapy (TCEL-4)

- **No response or progressive disease**
  - See Additional Therapy (TCEL-4)

**FOLLOW-UP THERAPY**

- Relapse, See Additional Therapy (TCEL-4)

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Peripheral T-Cell Lymphomas
excluding primary cutaneous T-cell lymphomas

RELAPSE/REFRACTORY DISEASE

ADDITIONAL THERAPY

RESPONSE #2

CONSOLIDATION/ADDITIONAL THERAPY

RELAPSE #2 OR GREATER

Candidate for high-dose therapy

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

Complete response or partial response

Not a candidate for high-dose therapy

Autologous stem cell transplant + involved field RT

Clinical trial or Clinical trial (including the option of allogeneic stem cell transplant)

Candidate for high-dose therapy

Clinical trial or Best supportive care

Clinical trial or Individual approach

Clinical trial or Best supportive care

No response

Clinical trial

Clinical trial

Clinical trial or Best supportive care

Candidate for high-dose therapy

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

Non candidate for high-dose therapy

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

Relapse/refractory disease

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TCEL-4
INTERNATIONAL PROGNOSTIC INDEX

**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

**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

---


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SUGGESTED TREATMENT REGIMENS
(in alphabetical order)

First-line therapy:
Clinical trial preferred
Aggressive regimens:
- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
- EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
- HyperCVAD/MTX-AraC

Note:
Intermediate and high risk patients (IPI) should be consolidated with high dose therapy and stem cell support (autologous or allogeneic)
ALK-1 ALCL is a subtype with good prognosis and do not need consolidative transplant if in remission.

Second-line therapy (with intent for stem cell rescue):
Clinical trial preferred
- DHAP (dexamethasone, cisplatin, cytarabine)
- ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)
- ICE (ifosfamide, carboplatin, etoposide)
- MiniBEAM (carmustine, etoposide, cytarabine, melphalan)
- MINE (mesna, ifosfamide, mitoxantrone, etoposide)

Second-line therapy (palliative intent):
- Denileukin diftitox
- Gemcitabine
- Alemtuzumab
- GDP (gemcitabine, dexamethasone, cisplatin)

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

**WORKUP**

**ESSENTIAL:**
- Biopsy of suspicious skin sites
- Dermatopathology review of slides

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Immunohistochemical studies of skin biopsy (CD2, CD3, CD4, CD5, CD7, CD8, CD26)
- Molecular study for T-cell receptor (TCR) gene rearrangements (assessment of clonality) of skin biopsy;
- PCR methods
- Assessment of peripheral blood for Sézary cells (in cases where skin is not diagnostic, especially T4) including Sézary cell prep, flow cytometry and PCR for TCR gene rearrangement
- Biopsy of suspicious lymph nodes

**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)

**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 lymph node regions
  - Palpation of organomegaly/masses
- Laboratory studies:
  - CBC with Sézary screen (manual slide review, "Sézary cell prep")
  - Sézary 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 Sézary Syndrome suspected

**Stage IA**
- See Primary Treatment (MFSS-2)

**Stage IB-IIA**
- See Primary Treatment (MFSS-3)

**Stage IIB**
- See Primary Treatment (MFSS-4)

**Stage III**
- See Primary Treatment (MFSS-5)

**Stage IV**
- See Primary Treatment (MFSS-6)

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**Notes:**
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- 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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**References:**

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**Additional notes:**
- Sézary syndrome (B2) defined by Sézary cell count ≥ 1,000/mL (Sézary cell prep) or expanded CD4+ cells with CD4/CD8 ratio ≥ 10, CD4+/CD7- ≥ 40%, or CD4+/CD26- ≥ 30% of lymphs in the presence of a positive clonal TCR gene rearrangement.
- Additional studies for related therapy: additional immunohistochemical studies - CD25, CD30 (targeted therapies), thyroid function studies (bexarotene therapy), lipid panel (systemic retinoid therapy).
**Mycosis Fungoides/Sezary Syndrome of the cutaneous T-cell lymphomas**

### Stage IA
- Skin-directed therapies (may be alone or in combination with other skin-directed therapies):
  - Topical corticosteroids
  - Topical chemotherapy (nitrogen mustard, BCNU)
  - Local radiation (particularly unilesional presentation)
  - Topical retinoids (bexarotene, tazarotene)
  - Phototherapy (UVB for patch/thin plaque disease; PUVA for thicker plaques)

### Stage IA with B1 blood involvement or histologic evidence of follicular or large cell transformed MF
- Combination skin-directed therapies (local RT to follicular or large cell transformed sites)
- Consider skin-directed therapy + systemic biologic therapy
- Total skin electron beam therapy (TSEBT) (reserved for patients with severe symptoms)

---

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Related Reading:
- [Clinical Trials](#)
- [Guidelines Index](#)
**Stage IB-IIA**

**Primary Treatment**

- Generalized skin treatment
  - Topical chemotherapy (nitrogen mustard, BCNU)
  - Phototherapy
    - UVB for patch/thin plaque disease
    - PUVA for plaque disease
  - TSEBT (if severe symptoms, generalized very thick plaques); may follow radiation course with topical or systemic biologic therapy ± adjuvant local skin treatment
  - (see stage IA on MFSS-2)

- Systemic therapy (single or ≥ 2 combination systemic treatments)
  - Interferon-alpha or gamma
  - Systemic retinoids (bexarotene, 13-cis, acitretin, all-trans retinoic acid)
  - HDAC inhibitor (vorinostat)
  - ECP if B1 blood involvement
  - Denileukin diftitox
  - Methotrexate (low-dose) ± skin-directed therapy
  - Clinical trial

**Relapse with T1-T2 disease:**
- T1 (see stage IA on MFSS-2)
- T2 (see generalized skin treatment)

**Refractory disease or progression on skin-directed therapies**

- Systemic chemotherapy agents used in stage IIB disease
- Liposomal doxorubicin
- Gemcitabine
- Methotrexate (high-dose)
- Clinical trial

**Stage IB-IIA with B1 blood involvement or histologic evidence of follicular or large cell transformed MF**

- TSEBT or Consider skin-directed therapy + systemic therapy (single or combination systemic therapies)

**Refractory disease or progression**

- Referral to a multidisciplinary academic specialty center preferred.
- For patients with recalcitrant sites after generalized skin treatment, additional local treatment may be needed.
- Low-dose methotrexate is ≤ 100 mg given oral, subcutaneous, or intravenous, every week.

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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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**Mycosis Fungoides/Sezary Syndrome**

**STAGE**

- **Limited extent tumor disease ± patch/plaque disease**
  - Local RT for limited tumor lesions + skin-directed therapies as in stages I-IIA

- **Generalized tumor disease or limited extent tumor disease with B1 or histologic evidence of follicular or large cell transformed MF**
  - Referral to a multidisciplinary academic specialty center preferred.
  - Other primary treatment options should be considered for patients not responsive to initial therapy before proceeding to therapy for refractory or progressive disease.
  - Patients achieving a response should be considered for maintenance or taper regimens to optimize response duration.

**PRIMARY TREATMENT**

- **Stage IIB**
  - Single-agent biologic therapies (bexarotene or other retinoids, interferons, denileukin diftitox) ± skin-directed therapy
  - HDAC inhibitor (vorinostat) ± skin-directed therapy
  - TSEBT + skin-directed or systemic therapy
  - Phototherapy + systemic biologic therapy (retinoid, interferon, vorinostat)
  - Systemic biologic combinations ± other skin directed therapies (see stage IA on MFSS-2 or stage IB-IIA on MFSS-3)
  - Retinoid + interferon
  - Retinoid + denileukin diftitox
  - ECP (if B1) + retinoid ± interferon

- **Refractory disease or progression**
  - CR
  - PR

- **Relapse with T1-T3 limited**
  - CR
  - PR

- **Relapse with T1-T3:**
  - T1-2 (see stage IA on MFSS-2 or stage IB-IIA on MFSS-3)
  - T3

- **Mult-agent chemotherapy**
  - Consider allogeneic transplant
  - Clinical trial

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**STAGE III**

- **B0** → Skin-directed therapy (see stage IA on MFSS-2 or stage IB-IIA on MFSS-3)
  - Extracorporeal photopheresis (ECP)
  - Interferon-alpha or gamma
  - Systemic retinoid
  - HDAC inhibitor (vorinostat)
  - Denileukin diftitox
  - Methotrexate (low-dose)

- **B1** → Systemic therapies (as above in B0) ± skin-directed therapy

**CR** → Relapse

**PR** → Refractory disease or progression

**Refractory disease or progression**

- Combination biologic therapies
  - ECP + interferon-alpha or gamma
  - ECP + systemic retinoid
  - ECP + systemic retinoid + interferon
  - Systemic retinoid + interferon
  - Bexarotene + denileukin diftitox

- Single agent chemotherapy
  - Methotrexate, gemcitabine, chlorambucil, liposomal doxorubicin, temozolomide, pentostatin
  - ± skin-directed therapy

**Refractory disease or progression**

- Alemtuzumab
- Consider non-ablative allogeneic transplant, as appropriate
- Clinical trial

---

**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.

---

**Referral to a multidisciplinary academic specialty center preferred.**

**Other primary treatment options should be considered for patients not responsive to initial therapy before proceeding to therapy for refractory or progressive disease.**

**Patients achieving a response should be considered for maintenance or taper regimens to optimize response duration.**

**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.**

**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 antibiotic therapy should be considered.**
Sezary syndrome ± lymph node disease

Low Sezary burden

- Combination biologic therapy
  - ECP + systemic retinoid ± interferon
  - Systemic retinoid (bexarotene) + denileukin difftox
- Single agent chemotherapy
  - Methotrexate
  - Gemcitabine
  - Chlorambucil
  - Liposomal doxorubicin
  - Temozolomide
  - Pentostatin
- HDAC inhibitor (vorinostat)

High Sezary burden

- Single agent or combination chemotherapy ± systemic biologic therapy ± RT ± skin-directed therapy
- Denileukin difftox

Stage IV

Bulky lymph node disease

Visceral disease (solid organ)

- Single agent or combination chemotherapy ± systemic biologic therapy ± RT ± skin-directed therapy
- Denileukin difftox

See Primary Treatment for Stage III (MFSS-5)

Refractory disease or progression

- Alemtuzumab
- Consider allogeneic transplant, as appropriate
- Clinical trial

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*Other primary treatment options should be considered for patients not responsive to initial therapy before proceeding to therapy for refractory or progressive disease.
*Patients achieving a response should be considered for maintenance or taper regimens to optimize response duration.
*All patients should be considered for clinical trials and referral for allogeneic HSCT. Ideal time for allo HSCT (preferably non-ablative) 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 allo HSCT is low. Patients should have failed biologic options and single agent chemotherapy prior to allo HSCT. When appropriate, TSEBT should be considered as cytoreductive therapy before transplant.

### RESPONSE CRITERIA FOR LYMPHOMA
(not including PET)

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Physical Examination</th>
<th>Lymph Nodes</th>
<th>Lymph Node Masses</th>
<th>Bone Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>CRu (unconfirmed)</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Indeterminate</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>Normal</td>
<td>&gt; 75% decrease</td>
<td>Normal or indeterminate</td>
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<tr>
<td>PR</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>≥ 50% decrease</td>
<td>≥ 50% decrease</td>
<td>Irrelevant</td>
</tr>
<tr>
<td></td>
<td>Decrease in liver/spleen</td>
<td>≥ 50% decrease</td>
<td>≥ 50% decrease</td>
<td>Irrelevant</td>
</tr>
<tr>
<td>Relapse/Progression</td>
<td>Enlarging liver/spleen, new sites</td>
<td>New or increased</td>
<td>New or increased</td>
<td>Reappearance</td>
</tr>
</tbody>
</table>


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.

See Response Designations and PET findings NHODG-A 2 of 2
<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
<th>Nodal Masses</th>
<th>Spleen, Liver</th>
<th>Bone Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>Disappearance of all evidence of disease</td>
<td>(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</td>
<td>Not palpable, nodules disappeared</td>
<td>Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative</td>
</tr>
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<td></td>
<td></td>
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</tr>
<tr>
<td>PR</td>
<td>Regression of measurable disease and no new sites</td>
<td>≥ 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</td>
<td>≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen</td>
<td>Irrelevant if positive prior to therapy; cell type should be specified</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>SD</td>
<td>Failure to attain CR/PR or PD</td>
<td>(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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapsed disease or PD</td>
<td>Any new lesion or increase by ≥ 50% of previously involved sites from nadir</td>
<td>Appearance of a new lesion(s) &gt; 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 &gt; 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy</td>
<td>&gt; 50% increase from nadir in the SPD of any previous lesions</td>
<td>New or recurrent involvement</td>
</tr>
</tbody>
</table>


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## Staging

### Table 1

**Proposed WHO Classification of Lymphoid Neoplasms**

### B-Cell Neoplasms
- **Precursor B-cell neoplasm**
  - Precursor B-lymphoblastic leukemia/lymphoma (precursor B-cell acute lymphoblastic leukemia)
- **Mature (peripheral) B-cell neoplasms**
  - B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
  - B-cell prolymphocytic leukemia
  - Lymphoplasmacytic lymphoma
  - Splenic marginal zone B-cell lymphoma (± villous lymphocytes)
  - Hairy cell leukemia
  - Plasma cell myeloma/plasmacytoma
  - Extranodal marginal zone B-cell lymphoma of MALT type
  - Nodal marginal zone B-cell lymphoma (± monocytoid B cells)
  - Follicular lymphoma
  - Mantle cell lymphoma
  - Diffuse large B-cell lymphoma
    - Mediastinal large B-cell lymphoma
    - Primary effusion lymphoma
  - Burkitt’s lymphoma/Burkitt cell leukemia

### T-Cell and NK-Cell Neoplasms
- **Precursor T-cell neoplasm**
  - Precursor T-lymphoblastic lymphoma/leukemia (precursor T-cell acute lymphoblastic leukemia)
  - Blastic NK-cell lymphoma/CD4+/CD56+ hematodermic neoplasm
- **Mature (peripheral) T-cell neoplasms**
  - T-cell prolymphocytic leukemia
  - T-cell granular lymphocytic leukemia
  - Aggressive NK-cell leukemia
  - Adult T-cell lymphoma/leukemia (HTLV1+)\(^b\)
  - Extramedullary T/NK-cell lymphoma, nasal type
  - Enteropathy-type T-cell lymphoma
  - Hepatosplenic T-cell lymphoma
  - Subcutaneous panniculitis-like T-cell lymphoma
  - Mycosis fungoides/Sézary syndrome
  - Anaplastic large-cell lymphoma, T/null cell, primary cutaneous type
  - Peripheral T-cell lymphoma, not otherwise characterized
  - Angioimmunoblastic T-cell lymphoma
  - Anaplastic large-cell lymphoma, T/null cell, primary systemic type

\(^a\)*B-cell and T-cell/NK-cell neoplasms are grouped according to major clinical presentations (predominantly disseminated/leukemic, primary extranodal, predominantly nodal).

\(^b\)*HTLV1+ indicates human T-cell leukemia virus; MALT, mucosa-associated lymphoid tissue; NK, natural killer.

## Table 2

**Cotswolds Modification of Ann Arbor Staging System**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Area of Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Single lymph node group</td>
</tr>
<tr>
<td>II</td>
<td>Multiple lymph node groups on same side of diaphragm</td>
</tr>
<tr>
<td>III</td>
<td>Multiple lymph node groups on both sides of diaphragm</td>
</tr>
<tr>
<td>IV</td>
<td>Multiple extranodal sites or lymph nodes and extranodal disease</td>
</tr>
<tr>
<td>X</td>
<td>Bulk &gt; 10 cm</td>
</tr>
<tr>
<td>E</td>
<td>Extranodal extension or single isolated site of extranodal disease</td>
</tr>
<tr>
<td>A/B</td>
<td>B symptoms: weight loss &gt; 10%, fever, drenching night sweats</td>
</tr>
</tbody>
</table>

An estimated 54,390 new cases of non-Hodgkin’s lymphoma (NHL), including 29,070 in men and 27,320 in women, were diagnosed in 2005, and 19,200 individuals with NHL died of the disease this year. NHL is the sixth leading site of new cancer cases among men and women, accounting for 4% of new cancer cases. NHL is also the 8th leading cause of cancer deaths among men and the 7th among women.¹

Non-Hodgkin’s lymphoma continues to increase in incidence. This increase is only in part explained by NHL developing in the setting of infection with human immunodeficiency virus (HIV). Much of the increase in incidence has been observed in patients in their sixth and seventh decades. The median age of individuals with NHL has risen in the last two decades from the late 50s to the early 60s.² As a result, patients with NHL may also have significant comorbid conditions, which complicate treatment options.

The non-Hodgkin's lymphomas may be classified on the basis of morphology, natural history, and immunophenotypic and molecular characteristics. The most recent World Health Organization (WHO) classification of NHL (Table 1) incorporates immunophenotypic and genetic information and includes several additional, newly identified entities not recognized by the International Working Formulation.³ 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 did investigate among 1,403 lymphoma cases for the thirteen most common histologic types that comprise about 90% of the cases of NHL in the United States.⁴ The findings were as follows: diffuse large B-cell, 31%; follicular lymphoma, 22%; small lymphocytic lymphoma (chronic lymphocytic leukemia), 6%; mantle cell lymphoma, 6%; peripheral T-cell lymphoma, 6%; and marginal zone B-cell lymphoma, mucosa-associated lymphoid tissue (MALT)-type, 5%. The remaining subtypes each occurred in less than 2% of cases. Composite lymphomas were not included in these distribution figures.

The National Comprehensive Cancer Network (NCCN) guidelines were developed for more common NHL histologic types - chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma, follicular lymphoma, and diffuse large B-cell lymphoma - and for less common entities with unique natural histories and therapies - marginal zone lymphoma (MZL), mantle cell lymphoma, and highly aggressive lymphoma subtypes, including Burkitt's, and lymphoblastic lymphomas as well as AIDS-related B-cell lymphomas. Separate
NCCN guidelines have not yet been developed for anaplastic T-cell and peripheral T-cell lymphomas. However, many NCCN investigators manage these diseases in the same way they treat aggressive diffuse large B-cell neoplasms (save for the inclusion of rituximab) or they place patients in a clinical trial.

Certain components of the diagnosis and therapy of the various non-Hodgkin’s lymphomas are similar. In all cases, the most important first step is to make an accurate pathologic diagnosis. An incisional or excisional lymph node biopsy is recommended to establish the diagnosis of NHL. Fine needle aspiration (FNA) is not considered adequate for an initial diagnosis of NHL (though it may be sufficient to establish relapse), and a core needle biopsy is discouraged unless the clinical situation dictates that this is the only safe means of obtaining diagnostic tissue. Recent studies show that FNA is not cost-effective and may misguide treatment. However, in certain circumstances, a combination of morphologic and flow cytometric studies may provide adequate information to provide a diagnosis. This is particularly true for the diagnosis of CLL. In other entities presenting in leukemic phase, eg. follicular lymphoma or mantle cell lymphoma, a biopsy is still preferred to clarify histological subtype.

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. Discussion of fertility issues and sperm banking ought to be performed under certain circumstances.

Each treatment guideline begins with the hematopathologic evaluation of the indicated entity (Diagnosis). Each guideline also includes the recommended staging studies (Workup) and therapeutic options at diagnosis and relapse (Therapy). The following summaries emphasize the unique aspects of the diagnosis, staging (Table 2), and treatment of the specific disease entities covered by the NCCN Non-Hodgkin’s Lymphoma Practice Guidelines.

**Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma**

**Diagnosis**

Chronic lymphocytic leukemia and small lymphocytic lymphoma (SLL/CLL type) are different manifestations of the same disease and are managed in much the same way. As with all the lymphoid neoplasms, adequate hematopathologic review is essential to establish an accurate diagnosis of CLL/SLL. Flow cytometric studies performed on patients with leukemic cell burden include kappa/lambda to access clonality. The typical immunophenotype in CLL/SLL are CD5+, CD19+, CD20 dim, CD23+, CD43+/−, CD10−, and cyclin D1−. Distinguishing CLL/SLL from mantle cell lymphoma is essential, as they are both CD5+ B-cell tumors. Cyclin D1− is critical in this differentiation of tumor types.

Additional paraffin-embedded material also should be available for immunophenotyping to determine lineage and clonality. A 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 are available in some laboratories to detect CD5, CD23, and cyclin D1. These can be useful, particularly for diagnosing SLL/CLL type without circulating cells.

Several markers have emerged as important prognostic factors in the outcome of CLL. Cytogenetic aberrations have important prognostic significance. FISH for abnormalities of 11q−, 13q−, +12 and 17p− (TP53) can be performed on fresh or paraffin-embedded
tissue. FISH for the t(11;14) chromosomal translocation can help distinguish mantle cell lymphoma (MCL) from CLL. Variable gene mutation status has been demonstrated to be a powerful predictor of outcome in CLL. However, determination of mutation status is not generally available as a clinical test.\(^9\)\(^,\)\(^10\) Evaluation of the expression of CD38 and/or Zap 70 has been proposed as surrogates for mutation status.\(^11\)\(^,\)\(^12\) Commercial reagents are now available for the evaluation of Zap 70 and may help determine prognosis in lieu of somatic variable gene mutation. The prognostic stratification for CLL provides useful information to determine favorable and unfavorable group of patients depending on FISH, gene mutation, and flow cytometry.

**Staging**

The Ann Arbor classification (see Table 2) has proven to be of limited usefulness in CLL because patients universally have bone marrow and peripheral blood involvement. In rare instances, patients may have nodal-only presentations of SLL. The modified Rai classification is most useful clinically and provides important prognostic information.\(^13\) Survival of patients with low-risk disease is essentially the same as the survival rate of age-matched controls. Patients with intermediate-risk disease have a shorter survival, particularly when other adverse factors coexist, such as a lymphocyte doubling time of less than 1 year. Patients with high-risk disease have a poor prognosis and typically require therapy at diagnosis.

**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 has been thought to have prognostic significance, this is no longer a factor when one uses more reliable prognostic markers such as Zap 70 or FISH. 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. The beta-2-microglobulin may have prognostic significance though whether or not this adds to the other factors is uncertain. Computed tomography (CT) scans or ultrasounds may be useful to follow and monitor disease progression when adenopathy is present. For anemic patients, reticulocyte counts and a direct Coombs' test should be performed to evaluate for the possibility of hemolysis.

**Therapy**

The induction therapy for CLL/SLL differs in patients who present with localized (Ann Arbor stage I-II) or advanced (Ann Arbor stage III-IV) disease. For patients with localized disease, either locoregional radiotherapy or observation is an appropriate option. Following disease progression, patients may be treated as needed for symptoms, threatened end-organ function, cytopenia, bulky disease at presentation, steady progression of disease, histologic transformation, and/or according to the patient's preference. In addition, because CLL/SLL is currently incurable with standard therapy, eligibility for a clinical trial is an important indication for therapy.

Patients who present with stage III-IV disease or whose disease is staged by other methods also are treated as needed in keeping with these indications. Patients with autoimmune cytopenia may need therapy directed at only the autoimmune process. Patients with recurrent infections, particularly those patients with encapsulated organisms and hypogammaglobulinemia, may benefit from intravenous gamma globulin.
Generally, patients with Rai good-risk disease do not meet the above criteria for treatment. By definition, patients with Rai high-risk disease are treated at presentation. Patients with Rai intermediate-risk disease can be observed unless they meet one of the above criteria.

Current options for systemic chemotherapy include the administration of an alkylating agent, a purine analog with or without rituximab, or an alkylating agent-based combination chemotherapeutic regimen. Tumor lysis syndrome prophylaxis should be considered during the treatment. Appropriate choices for first-line therapy include fludarabine with or without rituximab.\textsuperscript{14,15} The CALGB study of fludarabine versus chlorambucil demonstrated superiority in overall response rate (ORR) and progression-free survival (PFS) for the fludarabine as initial therapy compared to chlorambucil. The study had a crossover design and found no survival difference between the arms suggesting that in some circumstances, chlorambucil as initial therapy maybe appropriate. Other acceptable alkylator-based regimens include cyclophosphamide (with or without prednisone) and CVP (cyclophosphamide, vincristine, and prednisone). The MD Anderson Cancer Center has reported substantial activity for FCR (cyclophosphamide, fludarabine, with or without rituximab).\textsuperscript{16} In the sequence of FC studies, the addition of rituximab appears to result in superior failure-free survival. Using a historical control, analysis of recent sequential CALGB trials suggests that addition of rituximab to fludarabine prolongs progression-free and overall survival.\textsuperscript{17} Patients who achieve a complete or partial response are generally monitored and additional therapy should be given only in the context of a clinical trial (eg, high dose chemotherapy with stem cell support or antibody maintenance).

Treatment options for patients with disease progression are similar to those available as initial therapy. The choice of second-line therapy should take into account the remission duration as well as the initial agents used. In addition, alemtuzumab is approved for the therapy of relapsed and refractory CLL.\textsuperscript{18} CMV antigens should be monitored, when detected and the antiviral therapy considered. Therapy should continue regardless of intervention for CMV antigenemia.

The combination of pentostatin and cyclophosphamide with or without rituximab (PC±R) has shown significant activity in relapsed and refractory patients.\textsuperscript{19} Three forms of autoimmune cytopenia occur in CLL/SLL and may require targeted therapy. Initial therapy for autoimmune hemolytic anemia (AIHA) and immune thrombocytopenic purpura (ITP) is steroidal. Intravenous immunoglobulin may be used in the treatment of refractory disease. Rituximab and splenectomy is an option in select patients. Immunosuppressive agents such as prednisone, cyclosporine, and ATG (antithymocyte globulin) are indicated for the treatment of pure red cell aplasia.

**Follicular Lymphoma**

**Diagnosis**

Follicular lymphoma has a characteristic immunophenotype, which includes CD10+, bcl-2+, CD23+/-, CD43-, CD5-, CD20+, cyclin D1-, and bcl-2+ (\textasciitilde 90%). Rare cases of follicular lymphoma may be CD10-, or bcl-2-. 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. Additional paraffin-embedded material is useful,
under certain circumstances, for immunophenotyping to determine presence of bcl-6, cyclin D1 (if CD10- and/or CD5+ or CD43+), CD43, kappa/lambda, CD21, and MIB1(Ki-67). The diagnosis is generally easily established on histological grounds but immunophenotyping is encouraged to distinguish from a nodular MCL.

**Workup**

The diagnostic workup for follicular lymphoma is similar to the workup for other indolent lymphomas. The majority of patients present with disseminated disease. Because the approach to therapy differs dramatically between patients with localized and those with disseminated disease, particular attention should be paid to the presence or absence of bone marrow involvement. Bilateral bone marrow biopsies will increase the diagnostic yield. The FLIPI (Follicular Lymphoma International Prognostic Index) and GELF (Groupe d’Etude des Lymphomes Folliculaires) criteria may be used in determining treatment options.

In patients presenting with what appears to be localized disease, a PET scan may be helpful in identifying occult sites of disease. However, this remains to be verified in larger prospective series. The majority of NCCN investigators routinely employ chest, abdominal and pelvic CT as part of the diagnostic evaluation. PET scan is preferred in selected cases especially to rule out sites of histological transformation. Gallium-67 scan double dose with delayed images is useful as an alternative if PET is unavailable.

**Therapy**

The therapeutic approach to follicular lymphomas (grades 1 and 2, WHO classification) depends on the extent of initial disease involvement. Follicular large cell lymphomas (International Working Formulation) or follicular lymphomas, grade 3 (WHO/REAL classification) are generally treated according to the guidelines for diffuse large B-cell lymphoma, though they are recognized to have a much higher risk of relapse. It should also be noted that in most centers the proportion of patients diagnosed with FL, grade 3 is greater than that of follicular large cell lymphoma because the WHO classification utilizes the counting method of Berard. This impact of this change on the management of FL, grade 3 is unknown at the present time.

Patients with non-bulky localized (Ann Arbor stage I-II) follicular lymphoma are candidates for potentially curative locoregional radiation therapy (RT) with doses of 30 to 36 Gy, chemotherapy followed by RT (category 2B), or extended-field RT (category 2B). The addition of chemotherapy or more extended RT can improve failure-free survival but has not been shown to improve overall survival. In circumstances where toxicity of involved field RT (locoregional) outweighs the potential clinical benefit, observation is recommended. If patients relapse following localized RT or have no response to initial therapy, they should be managed in the same manner as patients with systemic presentation of follicular lymphoma.

Patients who present with localized (Ann Arbor stage II) bulky abdominal or stage III or IV disease, the decision to treat is based on the following indications: symptoms, threatened end-organ function, cytopenia secondary to lymphoma, bulky disease at presentation, steady progression of disease, and/or patient preference. Because follicular lymphoma is currently incurable with standard therapy, eligibility for a clinical trial is also an appropriate indication for therapy. Patients with indications for therapy should be treated in the context of a clinical trial when available. In the
absence of an appropriate clinical trial, numerous treatment options exist including locoregional RT and single agent or combination chemotherapy. The selection of treatment should be highly individualized taking into account age, extent of disease, comorbid conditions, and the goals of therapy. Single agent cyclophosphamide had equivalent long-term survival as combination chemotherapy. Single agent rituximab has moderate activity and this response duration can be extended by maintenance; however, no impact on survival has yet been demonstrated for maintenance. CVP chemotherapy has been standard treatment for follicular lymphoma though recently presented data demonstrated improvement in ORR and PFS with the addition of rituximab. Fludarabine-based combinations (F±R and FND±R (fludarabine, mitoxantrone, dexamethasone ± rituximab)) also have demonstrated activity but have not been shown to be superior alternative treatment. CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) combined with rituximab has been shown to produce long remission and a recent study demonstrated superiority to CHOP alone. However, the lack of a survival advantage and the early use of an anthracycline was not universally endorsed by the panel (category 2B). In addition, chlorambucil is also a recommended first-line therapy. In general, the addition or rituximab to chemotherapy regimens for follicular lymphoma has consistently improved the overall response rate, complete response rate and progression-free survival. However, clear evidence supporting a survival advantage is still lacking. Radioimmunotherapy (category 2B) or CHOP with or without rituximab followed by radioimmunotherapy (category 2B) are also recommended for initial therapy. It is strongly recommended that patients treated this way be included on a prospective on a prospective clinical study. 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. Patients who exhibit no indications for therapy may be followed expectantly.

Responding patients are usually followed until their disease recurs. At recurrence, biopsy is generally indicated to exclude histologic transformations, especially if there are rising LDH levels, disproportional growth in one area, development of extranodal disease, or new “B” symptoms develop. Biopsy of gallium avid areas should be targeted. If transformation to diffuse large B-cell lymphoma occurs and the patient has had minimal prior chemotherapy or did not have one, anthracycline-based therapy or chemotherapy ± rituximab are treatment options. This may be followed by consideration of either autologous or allogeneic hematopoietic stem cell transplantation.

At the time of relapse, the decision to treat is once again based on the clinical indications. Treatment options at relapse include those presented above as well as others. Two radioimmunotherapy agents, 90Y-ibritumomab tiuxetan and iodine-131-tositumomab/tositumomab, are available and have significant activity in the treatment of relapsed and refractory disease. High-dose therapy with an autologous or allogeneic source of stem cell support may also be an appropriate option for these patients. In the case of allogeneic stem cell transplants, nonmyeloablative approaches may be considered.

### Marginal Zone Lymphoma

Clinical and genetic features have demonstrated that the marginal zone lymphomas (MZL) are a heterogeneous group of disorders consisting of MALT lymphoma, nodal MZL, and splenic MZL. This
new understanding is reflected in the current practice guidelines. Nodal MZL is managed like other systemic indolent lymphomas (see Follicular Lymphoma). The MALT lymphomas are subdivided into the gastric versus non-gastric because of the association of the gastric MALT lymphoma with *Helicobacter pylori* (*H. pylori*) infection. In the gastric MALT lymphoma the *H. pylori* infection has a critical role in the pathogenesis of the disease and its eradication can lead to tumor remission. Other MZLs have been shown to be associated with chronic infection; however, tumor response based on treatment of the infection in most non-gastric MALT lymphoma remains anecdotal.

**Diagnosis**

Adequate hematopathology and immunophenotyping are needed to establish a diagnosis. The typical immunophenotype of MZL is CD5-, CD10-, CD20+, CD23-/+, cyclin D1-, bcl-2 follicles. In addition, a *Helicobacter pylori* stain is considered essential in gastric MALT lymphoma. Nondiagnostic atypical lymphoid infiltrates that are *H. pylori*-positive should be re-biopsied to confirm or exclude lymphoma prior to treatment of *H. pylori*. Molecular, cytogenetic, or FISH evaluation for the t(11;18) chromosomal translocation fusing the API2 and MALT1 genes can be helpful because the detection of this lesion is associated with antibiotic resistance in gastric MALT lymphoma. In selected cases endoscopy with multiple biopsies of anatomic sites is warranted.

**Gastric MALT Lymphoma**

**Workup**

The workup for gastric MALT lymphoma is similar to the workup for other non-Hodgkin's lymphomas. 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*. Appropriate imaging studies include CT of the chest, abdomen and pelvis, and in select cases, bone marrow biopsy. At some NCCN institutions, endoscopic ultrasound is used to complement conventional endoscopy at the time of the initial workup and at follow-up.

**Therapy**

As mentioned above, *H. pylori* infection plays a central role in the pathogenesis of some cases of gastric MALT lymphoma. The efficacy of antimicrobial therapy as treatment for gastric MALT lymphoma has been evaluated in numerous trials. Approximately two thirds of patients with localized gastric MALT lymphoma have a complete tumor remission after eradication of *H. pylori* infection with antibiotic therapy. However, there is increasing evidence that late relapses occur after antibiotic management and a long duration of follow-up is appropriate.

**Stages IE *H. pylori* positive**

For disease confined to the stomach, 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) chromosomal translocation, treatment of the *H. pylori* infection with antibiotics may be ineffective and treatment with involved field radiation therapy is appropriate.

**Stages IE or II *H. pylori* negative**

Because of the slow progression of disease and the difficulty in establishing an *H. pylori* infection, patients with stage IE *H. pylori*-negative or stage II disease could be treated with an empiric course of antibiotics and re-evaluated at 3 months with endoscopy.
Preferred method for these patients is involved field RT (30-33Gy) particular if a t(11;18) translocation is present.\textsuperscript{48} Rituximab is an option if radiation therapy is contraindicated.

**Endoscopic reevaluation after antibiotics**

For patients in whom antibiotic therapy was the primary treatment, 4 distinct outcomes can be observed. The first outcome includes patients who have both a microbiologic and tumor response, who are just observed. The second outcome includes patients who have no evidence of \textit{H. pylori} but who have persistent lymphoma. RT is indicated for patients with significant disease progression or symptoms. Either continued monitoring (with repeat endoscopy in 3 months) or locoregional RT is appropriate for the asymptomatic patients. RT can be considered as early as 3 months after observation, but observation can be prolonged for up to 18 months (category 2B). The third group includes patients with persistent \textit{H. pylori} and regressing or stable lymphoma who are treated with second-line antibiotics. The fourth outcome includes patients who are \textit{H. pylori} positive and have persistent lymphoma. Patients with progressive disease are treated with RT. Those with stable disease are treated with second-line antibiotics.

Follow-up surveillance consists of repeat endoscopy. Patients who exhibit microbiologic and complete tumor response continue to be observed. Patients with persistent or recurrent lymphoma and negative \textit{H. pylori} after antibiotic therapy are treated with locoregional RT if not previously treated. Patients whose disease does not respond to radiation may be treated with single-agent or combination chemotherapy. In general, surgery is reserved for patients with localized disease that has not responded to other therapeutic modalities.

**Stages III/IV**

In patients with disseminated disease, management is similar to the management of other advanced-stage indolent lymphomas. As with other indolent lymphoma, an asymptomatic patient without indication for therapy can be 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 combination or single-agent chemotherapy or locoregional RT (as per the follicular lymphoma guidelines). Given the incurability of conventional therapy, investigational therapy is considered as first-line therapy.

**Nongastric MALT Lymphomas**

Nongastric MALT lymphomas can arise from a large number of sites, including skin, lung, salivary gland (including parotid), conjunctiva, prostate, ovary, small bowel, and colon. For patients with stage IE or II disease, locoregional RT (20-30 Gy) is appropriate for those who may be curable. For certain sites of disease (eg, lung, skin, thyroid, colon, small intestine, breast), primary surgery is appropriate. For primary lymphomas of the breast, postoperative RT is often employed. Patients with advanced-stage disease (stage III-IV) are managed the same as patients with follicular lymphoma and the decision to treat is based on the same indications or locoregional RT is an option. Aggressive histologies, in which MALT lymphomas coexist with large cell lymphoma, should be managed according to the diffuse large B-cell practice guidelines.

**Splenic MZL**

**Diagnosis**

Splenic MZL is often presumptive based on the findings of
splenomegaly with peripheral blood flow cytometry usually revealing a monoclonal B cell population. 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.

**Therapy**

Patients who are positive for hepatitis C should have a hepatology consult to determine if there are indications for treatment of the viral infection. In cases where anti-virals are used to manage the hepatitis infection, the patient should be monitored for a tumor response. In all other patients, in the absence of cytopenias or symptoms, patients should be observed. For patients with cytopenias or symptoms of weight loss, early satiety or abdominal pain, splenectomy is indicated. Patients should be monitored on a regular basis. If the splenectomy is contraindicated or there is an evidence of recurrence, patients are managed as per the NCCN Follicular Lymphoma practice guidelines for advanced stage.

**Mantle Cell Lymphoma**

**Diagnosis**

As a consequence of widespread availability of appropriated diagnostic reagents, mantle cell lymphoma can be readily distinguished from other small lymphocytic lymphomas. The diagnosis can be established by histological examination in combination with immunohistochemistry with a profile consisting of CD5+, CD10-/+, CD20+, CD23-/+ (though + if rare cases), CD43+, and cyclin D1+. Rare cases of MCL may include CD5-immunophenotype. Yatabe et al have reported on a distinct outcome among patients in the cyclin D1-positive group and those in the cyclin D1-negative group, in which the expression of cyclin D1 was detected by immunohistochemistry. Therefore, it is now suggested that the diagnosis of MCL requires the expression of cyclin D1, an opinion shared by the panel. However, this remains unsettled as recent gene profiling data suggests that cyclin D1 expression may not be required for the molecular signature of MCL. Immunohistochemistry with cyclin D1 antibodies can be difficult and in some cases cytogenetics or FISH for the t(11;14), juxtaposing the cyclin D1 locus with the IgH locus can be diagnostically helpful.

**Workup**

The workup for mantle cell lymphoma is similar to the workup for many indolent lymphomas and certain aggressive lymphomas. Mantle cell lymphoma 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. Mantle cell lymphoma may present as
lymphomatous polyposis coli and colon involvement is common. In the current guideline, colonoscopy is now considered a routine part of the evaluation of MCL. 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.

**Therapy**

Mantle cell lymphoma has the worst characteristics of both indolent and aggressive non-Hodgkin’s lymphomas. Like many of the more common indolent lymphoid neoplasms, mantle cell lymphoma appears to be incurable with conventional chemotherapy. However, mantle cell lymphoma does not have an indolent natural history; rather, it has the shorter disease-free and overall survivals more characteristic of aggressive lymphomas. Therefore, there is no established standard of care.

In the absence of standard management for mantle cell lymphoma, patients with this disease should be referred for participation in prospective clinical trials. Few patients present with localized MCL and the available published literature on management is retrospective and anecdotal. Outside of a clinical trial the panel recommended either combined modality therapy or involved field radiation therapy though this was based on treatment principles as there was not data to guide these recommendations.

The overwhelming majority of patients with MCL will have advanced stage disease and require systemic therapy. For patients who do not have access to clinical trials for first line therapy, several regimens have shown significant activity including R-HyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with methotrexate and cytarabine, R-CHOP, and R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) though relapse is common with a median time of 15-18 months without adjuvant stem cell transplant (autologous or allogeneic). Initial remission should be followed by stem cell transplantation (category 2B) in eligible patients as this has been associated with some evidence of durable remission. Allogeneic stem cell transplant alone or in the context of a clinical trial is considered as the first line consolidation therapy.

The optimal approach to recurrent disease remains to be defined. For this reason, the entry of patients into clinical trials is strongly encouraged. Data has demonstrated a role for single agents such as cladribine and bortezomib. Combination such as cyclophosphamide and fludarabine, PCR (pentostatin, cyclophosphamide, rituximab), and FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab) also have activity. Marked anti-tumor activity has been shown for rituximab plus thalidomide in patients with relapsed/refractory MCL. Patients who obtain only a partial response to induction therapy are also appropriate candidates for clinical trials of high-dose therapy and additional therapeutic modalities. Radioimmunotherapy has shown to be active for both untreated and relapsed MCL.

**Diffuse Large B-Cell Lymphomas**

**Diagnosis**

Diffuse large B-cell lymphomas (DLBCL) are the most common lymphoid neoplasms in adults. Currently, the two other major categories of aggressive lymphomas, anaplastic large cell lymphoma and peripheral T-cell lymphoma, are also treated according to the DLBCL practice guidelines though rituximab is omitted from treatment regimens. Follicular lymphoma, grade 3, is
also managed according to the DLBCL algorithm, despite its distinct natural history and high risk of recurrence. Recent work with gene expression microarray analysis of DLBCL has revealed significant heterogeneity within this diagnosis; 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-.

**Workup**

Once the diagnosis is made, 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 (≤60 versus >60), stage of disease (CS I-II versus CS III-IV), serum lactate dehydrogenase (LDH) level (normal versus >normal), performance status (ECOG 0-1 versus ECOG 2-4), and the number of extra-nodal sites of disease (≤1 versus ≥2). The International Prognostic Index (IPI) can be used to identify patients who are more or less likely to be cured with standard therapy.

Certain radiographic studies, such as gallium-67 or PET scans (preferred), have a more clear-cut role in selected cases of DLBCL than in other lymphoid neoplasms. Gallium or PET scans are particularly informative in the initial staging and subsequent follow-up of DLBCL because they can distinguish residual fibrotic masses from masses containing viable tumor. 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). It is also indicated in the case of HIV-associated lymphoma.

**Therapy**

The realistic goal of induction therapy for DLBCL is to cure the disease. In fact, almost half of the patients with DLBCL may be cured with conventional therapy. Approaches to the treatment of DLBCL differ between patients with localized (Ann Arbor stage I-II) and advanced (Ann Arbor stage III-IV) disease.

In patients with localized disease, treatment approaches also differ between patients with non-bulky (<10 cm) disease and those with bulky (≥10 cm) and/or extranodal disease.

Patients with non-bulky localized disease who do not have adverse risk factors such as an elevated LDH, stage II disease, age >60 or an ECOG performance status ≥2 have an extremely good prognosis and may be treated with an abbreviated course (three cycles) of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) combined with involved-field RT. For patients with any of the adverse features listed above, the recommendation is 6-8 cycles of CHOP+R. Patients could receive additional adjuvant RT (category 2B). Patients who present with bulky disease and/or local extranodal disease may be more effectively treated with a full course (six to eight cycles) of CHOP chemotherapy with rituximab and involved-field RT (category 1).

Treatment options for patients with advanced-stage disease vary depending on additional prognostic information provided by the Age-Adjusted International Index. Patients who fall into the low- or low-intermediate risk category, as indicated by a normal LDH serum
level and normal performance status (Eastern Cooperative Oncology Group [ECOG] 0 or 1) are appropriate candidates for full-course anthracycline-based chemotherapy. This therapy would include six to eight cycles of R-CHOP for patients of all ages (category 1). An alternative is CHOP-14 (bi-weekly CHOP) for patient >60. However, 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 (ie, vigorous hydration and administration of allopurinol).

Patients who fall into the IPI high-intermediate- or high-risk category have less than a 50% chance of being cured with standard therapy. For this reason, the consensus of the panel is that, if possible, these patients should be treated in the context of appropriate clinical trials. Most current trials are evaluating augmented chemotherapy in the form of up-front or consolidative high-dose therapy, with or without stem cell rescue, in this patient group. In patients who are not candidates for placement on a clinical trial protocol or who do not have access to a protocol, an alternative would be 6-8 cycles of CHOP (category 1) with rituximab.

Patients who are receiving induction therapy should undergo repeat radiographic evaluation, including all positive studies, after three to four cycles of treatment. This early restaging is performed to identify, at the earliest point possible, patients whose disease has not responded or has progressed despite induction therapy. Upon completion of induction therapy, all positive radiographic studies should be repeated. Functional imaging (gallium or PET scans) may be particularly useful in determining whether residual masses represent fibrosis or viable tumor. A repeat biopsy of residual masses is recommended if the masses remained positive on a functional imaging scan upon completion of induction therapy.

For patients having complete response (CR) or complete response/unconfirmed (CRu), the planned course of treatment is completed. Consideration of autologous stem cell transplant or completing the course of therapy with a higher RT dose (40-45 Gy) is recommended for stage I-II patients with partial response (PR). Stage III-IV PR patients need to continue with R-CHOP to a total of 6-8 cycles. In addition, appropriate clinical trial is recommended for all the PR patients. If there is no response to treatment or progressive disease is observed, patients are treated as relapsed.

Patients who experience relapse following an initial complete response or have refractory disease and who are candidates for high-dose chemotherapy should be treated with a non-cross-resistant combination chemotherapeutic regimen, such as ICE±R (ifosfamide, carboplatin and etoposide), DHAP (dexamethasone, cytarabine, cytosine arabinoside, and cisplatin), MINE (mitoxantrone, ifosfamide, mesna, etoposide), miniBEAM (carmustine, etoposide, cytarabine, melphalan), and ESHAP (methylprednisolone, etoposide, cytarabine, cisplatin) in an attempt to achieve a second response. Patients who respond (CR or PR) to a non-cross-resistant chemotherapy regimen should be considered for further consolidation with high-dose therapy and stem cell support (category 1 for second response in relapse, category 2A for all others). There are multiple approaches to high-dose therapy with stem cell support; however, none of these has emerged as the preferred alternative. Additional RT can be given before or after stem cell transplant to sites of bulky disease. Pertinent clinical trials are considered another option in this case. Patients who achieve
complete remission and are not eligible for high-dose therapy should be treated individually.

Similarly, patients with disease recurrence following high-dose therapy should be treated in the context of a clinical trial or individually. However, patients with disease progression despite three successive chemotherapy regimens are not likely to benefit from currently available standard therapy, except for patients with a long disease-free interval.

Highly Aggressive Lymphomas

Burkitt's lymphoma (WHO classification) and 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. These diseases are aggressive B-cell tumors typically involving extranodal disease sites. For these reasons, these lymphomas are considered together in the treatment guidelines. 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.

Diagnosis

The typical immunophenotypes are as follows:

- Burkitt's: slg+, CD10+, CD20+, TdT-, Ki67+ (100%), bcl-2-
- Lymphoblastic B-cell: slg-, CD10+, CD19+. CD20-/+, TdT+ (unless they are BL or ALL-L3)
- Lymphoblastic T-cell: slg-, CD 10-, CD1a+/-, CD2+, CD3-/+,
  CD4/8+/-, CD7+, CD19/20-, TdT+

The cytogenetics of Burkitt's lymphoma typically involves a translocation of chromosome 8 [t(8;22); t(2;8), or t(8;14)]. The cytogenetics of lymphoblastic lymphomas can vary.

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's 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.

Therapy

Lymphoblastic and Burkitt's lymphomas pose a high risk for tumor lysis. For this reason, appropriate therapy includes allopurinol and hydration. The initial cycle of therapy should be administered on an inpatient basis. The subset of patients with Burkitt's lymphoma who have completely resected abdominal lesions or a single extra-abdominal mass and normal LDH level are considered to have low-risk disease. All others have high-risk disease. In certain recent treatment regimens, the intensity of therapy depends on whether patients have low- or high-risk disease. In recent years, the treatment of Burkitt's lymphoma with intensive short-course chemotherapy has proven successful. Options for induction therapy for Burkitt's lymphoma include clinical trial or combination chemotherapy regimens including intensive alkylating agents, anthracycline, intrathecal chemotherapy and high-dose methotrexate with or without rituximab. Patients with relapsed or refractory disease should be treated in the context of a clinical trial whenever possible.

In contrast, lymphoblastic lymphoma has generally been treated with regimens appropriate for acute lymphoblastic leukemia (ALL),
such as dose-intensive cyclophosphamide and anthracycline, standard-dose vincristine and asparaginase, and intrathecal chemotherapy. The CALGB ALL regimen has shown to be feasible in ALL treatment. Two short intensive regimens have also been demonstrated promising results in ALL therapy: 1) high-dose methotrexate with rituximab, and 2) high-dose cytarabine with rituximab. The combination chemotherapy using cytarabine with high-dose mitoxantrone, including intrathecal methotrexate has also shown activity in inducing complete remissions in ALL patients. Enrollment in clinical trials is encouraged to further refine these approaches and the most appropriate therapy should be chosen in consultation with an expert in lymphoma.

AIDS-Related B-Cell Lymphoma

Lymphoma developing in the setting of AIDS can take several forms: Burkitt's lymphoma, DLBCL, and primary CNS lymphoma. The patients who develop Burkitt's lymphoma generally have good CD4 counts though a small fraction may present with CD4<100. Primary CNS lymphoma develops in patients with very low CD4 counts and is most often seen in uncontrolled AIDS. The DLBCL occurs in the patients between these extremes. In the era of highly active antiretroviral therapy (HAART), the incidence of HIV-associated lymphoma has fallen. Overall, patients with HIV-associated lymphoma present with higher risk disease than matched patients with NHL without AIDS.

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's lymphoma and DLBCL. Hodgkin's disease and indolent lymphoma can be seen in HIV patients but are distinctly less common.

Workup

The diagnostic evaluation is as outlined above for DLBCL or Burkitt's 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.

Therapy

Optimal management of HIV-associated lymphoma has not been 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. Prophylactic therapy with intrathecal chemotherapy has also emerged as an important component of care. Patients with HIV-associated BL treated with CODOX-M/IVAC have outcomes similar to risk matched non-HIV patients. Patients with DLBCL should be treated with 6 cycles of full-dose CHOP. The omission of rituximab is strongly suggested for DLBCL patients with CD4<50 due to the higher risk of infectious toxicities. 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 filgrastim support. Rituximab appears to increase the risk of neutropenia and infection and there is no net benefit in patients with HIV-associated lymphoma.

Disclosures for the NCCN Non-Hodgkin's Lymphoma Guidelines Panel

At the beginning of each panel meeting to develop NCCN guidelines, panel members disclosed financial support they have
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Some panel members do not accept any support from industry. The panel did not regard any potential conflicts of interest as sufficient reason to disallow participation in panel deliberations by any member.
References


42. Arima N, Tsudo M. Extragastrointestinal mucosa-associated lymphoid tissue lymphoma showing the regression by Helicobacter pylori eradication therapy. Br J Haematol 2003;120:790-792.


62. 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


71. Forstpointner R, Dreyling M, Repp R et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared 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 Jul 29 [Epub ahead of print].


82. Habermann TM, Weller EA, Morrison VA et al. Phase III Trial of Rituximab-CHOP (R-CHOP) vs. CHOP with a Second Randomization to Maintenance Rituximab (MR) or Observation in Patients 60 Years of Age and Older with Diffuse Large B-Cell Lymphoma (DLBCL). Blood 2003;102:6a.


96. Hoelzer D, Baur K, Giagounidis A et al. Short intensive chemotherapy with rituximab seems successful in Burkitt NHL, Mature B-ALL and other high-grade B-NHL. Blood 2003;102(11)[abstract 236].


