Non-Hodgkin’s Lymphomas

Clinical Practice Guidelines in Oncology

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Overview

Non-Hodgkin’s lymphomas (NHLs) are a heterogeneous group of lymphoproliferative disorders originating in B-, T-, or natural killer (NK) lymphocytes. In the United States, B-cell lymphomas represent 80% to 85% of the cases, with 15% to 20% being T-cell lymphomas; NK lymphomas are rare. In 2010, an estimated 65,540 new cases of NHL were diagnosed and 20,210 patients died of the disease. NHL is the sixth leading site of new cancer diagnoses among men and women, accounting for 4% of new cancer cases and 4% of cancer-related deaths.
The incidence of NHL increased dramatically between 1970 and 1995, but has moderated since the mid-90s. This increase is attributed partly to the HIV epidemic and the development of AIDS-related NHL, but much of it has been observed in patients in their sixth and seventh decades. A large part of this increased incidence has paralleled a major decrease in mortality from other causes. The median age of individuals with NHL has risen in the past 2 decades. As a result, patients with NHL may also have significant comorbid conditions, which complicate treatment options.

NOTE: This manuscript highlights only a portion of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non-Hodgkin’s Lymphomas. Please refer to www.NCCN.org for the complete guidelines.

Classification

In 1956, Rappaport et al. proposed a lymphoma classification based on the pattern of cell growth (nodular or diffuse), and size and shape of the tumor cells. This classification, though widely used in the United States, quickly became outdated with the discovery and existence of distinct types of lymphocytes (B, T, and NK). The Kiel classification, which divided the lymphomas into low- and high-grade based on histologic features, became the first and most significant classification to apply this new information to lymphomas. This classification was widely used in Europe. However, the use of different classification systems in clinical studies made results difficult to compare. Hence, the International Working Formulation (IWF) for NHLs was developed to standardize the classification of lymphomas.

Text continues on p. 520

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**CLL/SLL**

**DIAGNOSIS**

### ESSENTIAL:
- Hematopathology review of all slides with at least one paraffin block representative of the tumor if the diagnosis was made on a lymph node or bone marrow biopsy. Rebiopsy if consult material is nondiagnostic.
- An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IGHV and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis. This is particularly true for the diagnosis of CLL/SLL.
- Flow cytometry of blood adequate for diagnosis of CLL/SLL (biopsy not required).
- Adequate immunophenotyping to establish diagnosis.
  - Recommended panel for paraffin section immunohistochemistry: CD3, CD5, CD10, CD20, CD23, cyclin D1
  - or
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10
- Absolute monoclonal B-lymphocyte count

### INFORMATIVE FOR PROGNOSTIC AND/OR THERAPY DETERMINATION:
- Cyto genetics and/or FISH to detect: t(11;14); t(11q;v); +12; del(11q); del(13q); del(17p)
- Molecular genetic analysis to detect: immunoglobulin heavy chain variable gene (IGHV) mutation status
- Determination of CD38 and ZAP-70 expression by flow cytometry or immunohistochemistry

**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 if CD20 monoclonal antibody contemplated
- MUGA scan/echocardiogram if anthracycline or anthracediones-based regimen is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

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

<table>
<thead>
<tr>
<th>Monoclonal B lymphocytosis (MBL)</th>
<th>CLL/SLL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute monoclonal B-lymphocyte count &lt; 5000/mm³</td>
<td>Observe</td>
</tr>
<tr>
<td>All lymph nodes &lt; 1.5 cm</td>
<td></td>
</tr>
<tr>
<td>No anemia</td>
<td></td>
</tr>
<tr>
<td>No thrombocytopenia</td>
<td></td>
</tr>
</tbody>
</table>

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**Notes:**

- **CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma. Cases diagnosed as B-PLL are excluded from this guideline.**
- **Typical immunophenotype: CD5+, CD23+, CD43+/−, CD10−, CD19+, CD20 dim, sIg dim+ and cyclin D1−. Note: Some cases may be sIg bright+, CD23− or dim and some MCL may be CD23+: cyclin D1 immunohistochemistry or FISH for t(11;14) should be considered in all cases and should be done in cases with an atypical immunophenotype (CD23 dim or negative, CD20 bright, sIg bright).**
- **See Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms (available online, in these guidelines, at www.NCCN.org [NHODG-A]).**
- **Absolute monoclonal B-lymphocyte count < 5000/mm³ in the absence of adenopathy or other clinical features of lymphoproliferative disorder is monoclonal B lymphocytosis (MBL).**
- **See Prognostic Information for CLL (page 491).**
- **Evaluation of ZAP-70 expression can be challenging and ZAP-70 is not recommended outside the setting of a clinical trial.**
- **Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.**

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

- Perform 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.

- Cell surface marker analysis by flow cytometry:
  - CLL/SLL: CD5+, CD23+, CD43+/-, CD10-, CD19+, CD20 dim, sIg dim+ and cyclin D1-. Note: Some cases may be sIg bright+, CD23- or cyclin D1 positive.

- Determination of CD38 and Zap-70 expression by immunohistochemistry or FISH for t(11;14) should be considered in all cases and in cases where transformation is suspected.

- Evaluate FISH for t(11;14); t(11q;v); +12; del(11q); del(13q); del(17p) to assist in directing nodal biopsy if Richter’s transformation is suspected.

- For CLL/SLL, absolute monoclonal B-lymphocyte count < 5000/mm³ is not generally nondiagnostic. However, CLL/SLL diagnosis may be sufficient for diagnosis. This is particularly true for the diagnosis of CLL/SLL.

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- Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consider prophylaxis for tumor lysis syndrome (available online, in these guidelines, at www.NCCN.org [NHODG-B]).

- Consider risk for CMV reactivation (see page 492).

- CLL/SLL with 11q deletion (see page 488)

- CLL/SLL with deletion of 17p (see page 489)

- CLL/SLL with deletion of 11q (see page 490)

- Manage as aggressive lymphoma (see pages 511 and 512)

- Consider allogeneic stem cell transplant (see pages 511 and 512)

- Evaluate for indications for treatment:
  - Eligible for clinical trial
  - Significant disease-related symptoms:
    - Fatigue (severe)
    - Night sweats
    - Weight loss
    - Fever without infection
  - Threatened end-organ function
  - Progressive bulky disease (spleen > 6 cm below costal margin, lymph nodes > 10 cm)
  - Lymphocyte doubling time (LDT) ≤ 6 mo
  - Progressive anemia
  - Progressive thrombocytopenia

- No indication

- Observation

- Indication present

- Evaluate FISH

- Imaging as appropriate

- CLL/SLL with Rai low (0) and intermediate (I-II) risk

- CLL/SLL with Rai high (III-IV) risk

- CLL/SLL with histologic transformation to diffuse large-cell/Hodgkin lymphoma

- SLL

- SLL/localized (Ann Arbor stage I)

- Locoregional RT (if indicated)

- Observe

- Consider prophylaxis for tumor lysis syndrome (available online, in these guidelines, at www.NCCN.org [NHODG-B])

- Consider risk for CMV reactivation (see page 492)

- Consider allogeneic stem cell transplant (see pages 511 and 512)

- CLL/SLL with deletion of 11q (see page 490)

h See Supportive Care For Patients With CLL (page 492).

i See Rai and Binet Classification Systems (page 491).

j Absolute lymphocyte count alone is not an indication for treatment unless above 200-300 x 10⁹/L or symptoms related to leukostasis.

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

l Platelet counts >100,000 cells/mm³ are typically not associated with clinical risk.

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

n In addition to the regimens listed on pages 511 and 512, R-hyperCVAD has also been used in this setting.

CLL WITHOUT DELETION OF 11q or 17p

FIRST-LINE THERAPY

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

See Suggested Regimens (page 493)

Long response > 3 y, repeat FISH, if del(17p)
see page 489, or del(11q)
see page 490

Retreat with first-line therapy until a short response

Consider allogeneic stem cell transplant, if
without significant comorbidities

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

Age ≥ 70 y or younger patients with comorbidities

See Suggested Regimens (page 493)

Short response < 2 y, repeat FISH, if del(17p)
see page 489, or del(11q)
see page 490

See Suggested Regimens (page 493; relapsed/refractory therapy)

Consider allogeneic stem cell transplant, if
without significant comorbidities

Age < 70 y or older without significant comorbidities

See Suggested Regimens (page 493)

Long response > 3 y, repeat FISH, if del(17p)
see page 489, or del(11q)
see page 490

Retreat with first-line therapy until a short response

Allogeneic stem cell transplant

RESPONSE TO THERAPY

Consider prophylaxis for tumor lysis syndrome (available online, in these guidelines, at www.NCCN.org [NHODG-B])

Consider risk for CMV reactivation (see page 492)

9

Absolute lymphocyte count alone is not an indication for treatment unless above 200-300 × 10^9/L or in the presence of symptoms related to leukostasis.


If long response, treat with the same first-line therapy. If short response, consider alternative first-line therapy not used before.

8See Supportive Care For Patients With CLL (page 492).

7See Suggested Regimens (page 493)

6See Suggested Regimens (page 494)

5See Suggested Regimens (page 494)
CLL WITH DELETION OF 17p

CLL with del(17p)\(^h, j, r\) →
- Clinical trial
  - del(17p) is associated with low response rates with all treatments and there is no standard treatment, clinical trial is recommended
- See Suggested Regimens (page 494)

CLL/SLL

**FIRST-LINE THERAPY**

RESPONSE TO THERAPY

- CR\(^h\)
  - Observe or Clinical trial
- PR\(^h\)
  - Observe or Clinical trial or See Suggested Regimens (page 494)
- No response
  - Clinical trial or Relapsed/refractory therapy (See Suggested Regimens, page 494)

- Observe

- Observe or Clinical trial or See Suggested Regimens (page 494)

- Candidate for transplant → Allogeneic stem cell transplant
- Noncandidate for transplant

**Consider prophylaxis for tumor lysis syndrome (available online, in these guidelines, at www.NCCN.org [NHODG-B])**

**Consider risk for CMV reactivation (see page 492)**

\(^h\)See Supportive Care For Patients With CLL (page 492).
\(^j\)Absolute lymphocyte count alone is not an indication for treatment unless above 200-300 x 10\(^9\)L or in the presence of symptoms related to leukostasis.
\(^r\)Patients with low positivity should be retested because of chance for false-positive results.
\(^s\)See Response Criteria: CLL (page 497) or SLL (available online, in these guidelines, at www.NCCN.org [NHODG-C]).

**CLL WITH DELETION OF 11q**

- Outcomes are more favorable in patients with del(11q) who receive regimens containing an alkylator

**FIRST-LINE THERAPY**

- Clinical trial
  - See Suggested Regimens (page 495)

**RESPONSE TO THERAPY**

- CR<sup>s</sup>
  - Observe or Clinical trial
- PR<sup>s</sup>
  - Consider allogeneic stem cell transplant
  - Observe or Clinical trial or See Suggested Regimens (page 495)
- No response
  - Candidate for transplant
  - Consider prophylaxis for tumor lysis syndrome (available online, in these guidelines, at www.NCCN.org [NHODG-B])
  - Consider risk for CMV reactivation (see page 492)
- No transplant
  - Noncandidate for transplant
  - Clinical trial or Relapsed/refractory therapy (See Suggested Regimens, page 495)

- CR<sup>s</sup>
  - Observe or Clinical trial
- PR<sup>s</sup>
  - No response

<sup>h</sup>See Supportive Care For Patients With CLL (page 492).

<sup>i</sup>Absolute lymphocyte count alone is not an indication for treatment unless above 200-300 x 10<sup>9</sup>/L or symptoms related to leukostasis.

<sup>j</sup>See Response Criteria: CLL (page 497) or SLL (available online, in these guidelines, at www.NCCN.org [NHODG-C]).
**Non-Hodgkin’s Lymphomas Version 2:2011**

**Prognostic Information for CLL**

**Immunoglobulin Variable Region (IGHV) Gene Mutation and Surrogates by Flow Cytometry**

<table>
<thead>
<tr>
<th>Outcome Association</th>
<th>Favorable</th>
<th>Unfavorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA sequencing&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&gt; 2% mutation</td>
<td>≤ 2% mutation</td>
</tr>
<tr>
<td>IGHV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow Cytometry</td>
<td>&lt; 30%</td>
<td>≥ 30%</td>
</tr>
<tr>
<td>CD38</td>
<td>&lt; 20%</td>
<td>≥ 20%</td>
</tr>
<tr>
<td>Zap-70</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Interphase Cytogenetics (FISH)<sup>b</sup>**

<table>
<thead>
<tr>
<th>Unfavorable</th>
<th>Neutral</th>
<th>Favorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>del(11q)</td>
<td>Normal</td>
<td>del(13q)</td>
</tr>
<tr>
<td>del(17p)</td>
<td>+12</td>
<td>(as a sole abnormality)</td>
</tr>
</tbody>
</table>

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

<sup>b</sup>IGHV rearrangements involving VH3-21 carry a poor prognosis even if mutated.

<sup>c</sup>Formal studies identifying the percentage of abnormal cells identified by FISH are ongoing, although populations < 10% appear to not have the clinical impact as noted in the table.

**CLL Staging Systems**

<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>Low</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>


<sup>c</sup>Immune-mediated cytopenias are not the basis for these stage definitions.
### SUPPORTIVE CARE FOR PATIENTS WITH CLL

| Recurrent sinopulmonary Infections (requiring intravenous antibiotics or hospitalization) | • Antimicrobials as appropriate  
• Evaluate serum IgG, if < 500 mg/dL  
  ▶ Begin monthly IVIG 0.3-0.5 g/kg  
  ▶ Adjust dose/interval to maintain nadir level of approximately 500 mg/dL. |
| --- | --- |
| Antiinfective prophylaxis | • Recommended for patients receiving purine-analog and/or alemtuzumab during treatment and thereafter, if tolerated  
  ▶ Herpes virus (acyclovir or equivalent)  
  ▶ PCP (sulfamethoxazole/trimethoprim or equivalent)  
• Alemtuzumab: clinicians must be aware of the high risk of CMV reactivation. The current appropriate management is controversial, some use ganciclovir (oral or intravenous) prophylactically if viremia present, others only if viral load is rising. CMV viremia should be measured by PCR quantitation at least every 2-3 wk. Consultation with an infectious disease expert may be necessary. |
| Autoimmune cytopenias | • Autoimmune hemolytic anemia (AIHA): diagnosis with reticulocyte count, haptoglobin, DAT  
  ▶ AIHA that develops in setting of treatment with fludarabine, stop, treat, and avoid subsequent fludarabine  
• Immune thrombocytopenia purpura (ITP): evaluate bone marrow for cause of low PLT  
• Pure red blood cell aplasia (PRCA): evaluate for parvo B19 and bone marrow evaluation  
• Treatment: corticosteroids; rituximab; IVIG; cyclosporin A; splenectomy; eltrombopag or romiplostim (ITP) |
| Vaccination | • Annual Influenza vaccine\(^a\)  
• Pneumococcal vaccine (Prevnar preferred) every 5 y  
• Avoid all live vaccines, including Zoster |
| Blood product support | • Transfuse according to institutional or published standards  
• Irradiate all blood products to avoid transfusion associated GVHD |

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\(^a\)In patients who have received rituximab, B-cell recovery occurs by approximately 9 mo. Before B-cell recovery, patients generally do not experience response to influenza vaccine, and patients who receive it should not be considered vaccinated.
## Suggested Treatment Regimens

**SUGGESTED TREATMENT REGIMENS**

*in order of preference*

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

<table>
<thead>
<tr>
<th>Frail Patient, Significant Comorbidity (not able to tolerate purine analogs)</th>
<th>First-Line Therapy</th>
<th>Relapsed/Refractory Therapy</th>
</tr>
</thead>
</table>
| • Chlorambucil ± prednisone | Age ≥ 70 y or younger patients with comorbidities  
  > Chlorambucil ± prednisone  
  > BR (bendamustine, rituximab)  
  > Cyclophosphamide, prednisone ± rituximab  
  > Alemtuzumab  
  > Rituximab  
  > Fludarabine ± rituximab  
  > Cladribine | Long response > 3 y  
  > Re-treat as in first-line therapy until short response |
| • Rituximab (single) | Age < 70 y or older patients without significant comorbidities  
  > Chemoimmunotherapy  
  > FCR (fludarabine, cyclophosphamide, rituximab)  
  > FR (fludarabine, rituximab)  
  > PCR (pentostatin, cyclophosphamide, rituximab)  
  > BR | Short response < 2 y for age ≥ 70 y  
  > Chemomunotherapy  
  > Reduced-dose FCR  
  > Reduced-dose PCR  
  > Bendamustine ± rituximab  
  > HDMP (high-dose methylprednisolone) + rituximab  
  > Chlorambucil ± prednisone (if used first-line)  
  > Ofatumumab  
  > Alemtuzumab ± rituximab  
  > Dose-dense rituximab (category 2B) |
| • Pulse corticosteroids | | Short response < 2 y for age < 70 y or older patients without significant comorbidities  
  > Chemoimmunotherapy  
  > FCR  
  > PCR  
  > BR  
  > Fludarabine ± alemtuzumab  
  > CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab  
  > HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab  
  > Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab  
  > OFAR (oxaliplatin, fludarabine, cytarabine, rituximab)  
  > Ofatumumab  
  > Alemtuzumab ± rituximab  
  > HDMP + rituximab |

See Monoclonal Antibody Directed at CD20 and Viral Reactivation (available online, in these guidelines, at www.NCCN.org [NHODG-D])

See Suggested Regimens for CLL with del(17p) (page 494)

See Suggested Regimens for CLL with del(11q) (page 495)

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*aSee references for regimens page 496.

bAntibiotic prophylactic therapy for shingles and pneumocystis is recommended in purine analog-based and/or alemtuzumab combination therapy.

cLess effective for bulky (> 5 cm) lymphadenopathy; monitor for CMV reactivation.

dMonitor for myelosuppression.

*Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.*
SUGGESTED TREATMENT REGIMENSA
(in order of preference)

CLL with del(17p)

**First-Line Therapy**
- FCR (fludarabine, cyclophosphamide, rituximab)
- FR (fludarabine, rituximab)
- HDMP (high-dose methylprednisolone) + rituximab
- Alemtuzumab ± rituximab
- Bendamustine ± rituximab

**Relapsed/Refractory Therapy**
- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab
- CFAR (cyclophosphamide, fludarabine, alemtuzumab, rituximab)
- HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab
- OFAR (oxaliplatin, fludarabine, cytarabine, rituximab)
- Ofatumumab
- Alemtuzumab ± rituximab
- High-dose dexamethasone ± rituximab
- Bendamustine ± rituximab

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See Monoclonal Antibody Directed at CD20 and Viral Reactivation
(available online, in these guidelines, at www.NCCN.org [NHODG-D])

See Suggested Regimens for CLL without del(11q) or del(17p) (page 493)

See Suggested Regimens for CLL with del(11q) (facing page)

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**a**See references for regimens on page 496.

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**d**Monitor for myelosuppression.

**e**Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.

**f**This is not effective in patients with lymph nodes > 5 cm.

**g**Rituximab should be added unless patient is known to be refractory to rituximab.
### SUGGESTED TREATMENT REGIMENS

**(in order of preference)**

**CLL with del(11q)**

<table>
<thead>
<tr>
<th>First-Line Therapy</th>
<th>Relapsed/Refractory Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 70 y or younger patients with comorbidities</td>
<td>Long response &gt; 3 y</td>
</tr>
<tr>
<td>● Chlorambucil ± prednisone</td>
<td>▶ Re-treat as in first-line therapy until short response</td>
</tr>
<tr>
<td>● BR (bendamustine, rituximab)</td>
<td></td>
</tr>
<tr>
<td>● Cyclophosphamide, prednisone ± rituximab</td>
<td></td>
</tr>
<tr>
<td>● Reduced-dose FCR (fludarabine, cyclophosphamide, rituximab)</td>
<td></td>
</tr>
<tr>
<td>● Alemtuzumab</td>
<td></td>
</tr>
<tr>
<td>● Rituximab</td>
<td></td>
</tr>
<tr>
<td>Age &lt; 70 y or older patients without significant comorbidities</td>
<td>Short response &lt; 2 y for age ≥ 70 y</td>
</tr>
<tr>
<td>● Chemoimmunotherapy</td>
<td></td>
</tr>
<tr>
<td>● FCR</td>
<td></td>
</tr>
<tr>
<td>● BR</td>
<td></td>
</tr>
<tr>
<td>● PCR (pentostatin, cyclophosphamide, rituximab)</td>
<td></td>
</tr>
<tr>
<td>See Monoclonal Antibody Directed at CD20 and Viral Reactivation (available online, in these guidelines, at <a href="http://www.NCCN.org">www.NCCN.org</a> [NHODG-D])</td>
<td>See and Viral Reactivation (available online, in these guidelines, at <a href="http://www.NCCN.org">www.NCCN.org</a> [NHODG-D])</td>
</tr>
<tr>
<td>See Suggested Regimens for CLL without del(11q) or del(17p) (page 493)</td>
<td>See Suggested Regimens for CLL with del(17p) (previous page)</td>
</tr>
</tbody>
</table>

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**a**See references for regimens on page 496.

**b**Antibiotic prophylactic therapy for shingles and pneumocystis is recommended in purine analog-based and/or alemtuzumab combination therapy.

**c**Less effective for bulky (> 5 cm) lymphadenopathy; monitor for CMV reactivation.

**d**Monitor for myelosuppression.

**e**Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.
SUGGESTED TREATMENT REGIMENS

References

Alemuzumab


Alemtuzumab + Rituximab

Bendamustine

Bendamustine + Rituximab

Chlorambucil


Chlorambucil + Prednisone

Cyclophosphamide, Fludarabine, Alemtuzumab, and Rituximab (CFAR)

CHOP (Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone)

FCR (Fludarabine, Cyclophosphamide, and Rituximab)


Fludarabine + Alemtuzumab

Fludarabine + Rituximab

HDMFP(High-Dose Methyprednisolone) + Rituximab


Ofatumumab


OFAR (Oxaliplatin, Fludarabine, Cytarabine, and Rituximab)


PCER (Pentostatin, Cyclophosphamide, and Rituximab)

**Non-Hodgkin’s Lymphomas Version 2:2011**

### RESPONSE DEFINITION AFTER TREATMENT FOR CLL

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

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

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

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Molecular genetic analysis to detect: antigen gene receptor rearrangements; BCL2 rearrangement
- Cytogenetics or FISH: t(14;18); t(8;14) or variants
- Paraffin section immunohistochemistry: Ki67

**WORKUP**

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

**USEFUL IN SELECTED CASES:**
- MUGA scan/echocardiogram if anthracycline or anthracycline-based regimen is indicated
- Neck CT
- Beta-2-microglobulin
- PET-CT scan
- Uric acid
- Discussion of fertility issues and sperm banking
- SPEP and/or quantitative immunoglobulin levels
- Hepatitis C testing

---

*a* Follicular lymphoma, grade 1-2. Follicular lymphoma, grade 3 is an area of controversy. The distinction between follicular grade 3a and 3b has not been shown to have clinical significance to date. Follicular lymphoma, grade 3 is commonly treated according to the guidelines for diffuse large B-cell lymphoma (DLBCL; page 505). Any area of DLBCL in a follicular lymphoma of any grade should be diagnosed and treated as a DLBCL.

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

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

*d* See Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms (available online, in these guidelines, at www.NCCN.org [NHODG-A]).

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

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

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

*h* Bilateral or unilateral provided core biopsy is > 2 cm. If radioimmunotherapy is considered, bilateral cores are recommended and the pathologist should provide the percent of overall cellular elements and the percent of cellular elements involved in the marrow. If observation is initial therapy, bone marrow biopsy may be deferred.
**FOLLICULAR LYMPHOMA (GRADE 1–2)**

### Staging and Initial Therapy

<table>
<thead>
<tr>
<th>Stage</th>
<th>Initial Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>I, II</td>
<td>IFRT&lt;sup&gt;1&lt;/sup&gt; (preferred for clinical stage I or contiguous stage II) or Immunotherapy ± chemotherapy (See pages 503 and 504) ± RT (category 2B for chemotherapy + RT)&lt;sup&gt;2&lt;/sup&gt; or Observation (selected cases)&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>I, II</td>
<td>Complete response&lt;sup&gt;4&lt;/sup&gt; or partial response&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>I, II</td>
<td>No response</td>
</tr>
<tr>
<td>I, II</td>
<td>No indication</td>
</tr>
<tr>
<td>I, II</td>
<td>Indications for treatment:&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stage I, II</td>
<td></td>
</tr>
<tr>
<td>I, II</td>
<td></td>
</tr>
<tr>
<td>I, II</td>
<td>See Suggested Regimens (pages 503 and 504) or Clinical trial&lt;sup&gt;11&lt;/sup&gt; or Local RT (palliation of locally symptomatic disease)</td>
</tr>
<tr>
<td>I, II</td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup>When determining initial treatment, consider excluding profoundly myelotoxic regimens for patients who may be eligible for high-dose therapy with autologous stem cell rescue.

<sup>2</sup>See Principles of Radiation Therapy (available online, in these guidelines, at www.NCCN.org [NHODG-E]).

<sup>3</sup>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.

<sup>4</sup>Observation may be appropriate in circumstances when toxicity of involved-field RT outweighs potential clinical benefit.

<sup>5</sup>See GELF criteria (page 502).

<sup>6</sup>Given incurability with conventional therapy, consider investigational therapy as first-line of treatment.

<sup>7</sup>See Response Criteria for Lymphoma (available online, in these guidelines, at www.NCCN.org [NHODG-C]).

<sup>8</sup>Follow-up includes repeat diagnostic tests, including imaging (based on site of disease and clinical presentation) as clinically indicated.

<sup>9</sup>Consider clinical trials appropriate for patients on observation.

<sup>10</sup>Progressive disease should be histologically documented to rule out transformation (preferentially, biopsy or marked increase in FDG uptake on PET), especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, new B symptoms develop, or there is marked heterogeneity or sites of intense FDG avidity on PET scan. A directed biopsy should be performed of a suspicious area. If transformation is histologically confirmed, treat with anthracycline-based therapy. Positive functional imaging does not replace biopsy to diagnose transformation. See Management of Transformation (page 501).

INITIAL RESPONSE

- Complete response or partial response
  - Consolidation or extended therapy (See pages 503 and 504) or Observe
  - Clinical follow-up every 3-6 mo for 5 y and then yearly or as clinically indicated

- Progressive disease (For transformation, see page 501)
  - Indications for treatment:
    - Candidate for clinical trial
    - Symptoms
    - Threatened end-organ function
    - Cytopenia secondary to lymphoma
    - Bulky disease
    - Steady progression
    - Patient preference
  - No indication
  - Observe

- No response or progressive disease (For transformation, see page 501)
  - See Suggested Regimens (pages 503 and 504) or Clinical trial or Local RT (palliation of locally symptomatic disease)
  - Indication present
  - Clinical trial

ADDITIONAL THERAPY

- Observation

See Principles of Radiation Therapy (available online, in these guidelines, at www.NCCN.org [NHODG-E]).

See GELF criteria (page 502).

See Response Criteria for Lymphoma (available online, in these guidelines, at www.NCCN.org [NHODG-C]).

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

Progressive disease should be histologically documented to rule out transformation (preferentially, biopsy or marked increase in FDG uptake on PET), especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, new B symptoms develop, or there is marked heterogeneity or sites of intense FDG avidity on PET scan. A directed biopsy should be performed of a suspicious area. If transformation is histologically confirmed, treat with anthracycline-based therapy. Positive functional imaging does not replace biopsy to diagnose transformation. See Management of Transformation (page 501).

Clinical trials may involve novel agents, regimens, or transplantation.

Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.
Progressive disease or transformation (see page 501)

Complete response or partial response

No response or progressive disease, or transformation (see page 501)

INITIAL RESPONSE

Observe

No indication

Indication present

ADDITIONAL THERAPY

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

Clinical trials may involve novel agents, regimens, or transplantation. See Principles of Radiation Therapy (available online, in these guidelines, at www.NCCN.org [NHODG-E]).

See GELF criteria (page 502).

See Response Criteria for Lymphoma (NHODG-C).

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

Progressive disease should be histologically documented to rule out transformation (preferentially, biopsy or marked increase in FDG uptake on PET), especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, new B symptoms develop, or there is marked heterogeneity or sites of intense FDG avidity on PET scan. Directed biopsy should be performed of a suspicious area. If transformation is histologically confirmed, treat with anthracycline-based therapy. Positive functional imaging does not replace biopsy to diagnose transformation. See Management of Transformation (page 501).

Multiple prior therapies

Histological transformation to diffuse large B-cell lymphoma

Minimal or no prior chemotherapy

HISTOLOGICAL TRANSFORMATION TO DIFFUSE LARGE B-CELL LYMPHOMA

Clinical trial or Radioimmunotherapy or Chemotherapy (See pages 511 and 512) ± rituximab or IFRT or Best supportive care (See NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] for Palliative Care*)

Responsive disease

Consider high-dose therapy with autologous stem cell rescue or allogeneic stem cell transplant*

Complete response

Observation or Clinical trial or Consider high-dose therapy with autologous stem cell rescue or allogeneic stem cell transplant*

Partial response

Consider high-dose therapy with autologous stem cell rescue or allogeneic stem cell transplant* or Clinical trial or Consider radioimmunotherapy

No response or progressive disease

Clinical trial or Radioimmunotherapy or Palliative or best supportive care

*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

1 See Response Criteria for Lymphoma (available online, in these guidelines, at www.NCCN.org [NHODG-C]).

2 Involved-field RT alone or one course of single agent therapy including rituximab.

3 If locoregional transformation, consider adding RT.

4 Strongly recommend this treatment be given in the context of a clinical trial; nonmyeloablative approaches may also be considered.

Mannequin used for counting the number of involved areas. The map is used to determine number of nodal sites in FLIPI-1 criteria and is different than the conventional Ann Arbor site map.

<table>
<thead>
<tr>
<th>GELF CRITERIA&lt;sup&gt;a,b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Involvement of ≥ 3 nodal sites, each with a diameter of ≥ 3 cm</td>
</tr>
<tr>
<td>• Any nodal or extranodal tumor mass with a diameter of ≥ 7 cm</td>
</tr>
<tr>
<td>• B symptoms</td>
</tr>
<tr>
<td>• Splenomegaly</td>
</tr>
<tr>
<td>• Pleural effusions or peritoneal ascites</td>
</tr>
<tr>
<td>• Cytopenias (leukocytes &lt; 1.0 x 10&lt;sup&gt;9&lt;/sup&gt;/L and/or platelets &lt; 100 x 10&lt;sup&gt;9&lt;/sup&gt;/L)</td>
</tr>
<tr>
<td>• Leukemia (&gt; 5.0 x 10&lt;sup&gt;9&lt;/sup&gt;/L malignant cells)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FLIPI-1 CRITERIA&lt;sup&gt;a,c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td><strong>Ann Arbor stage</strong></td>
</tr>
<tr>
<td><strong>Hemoglobin level</strong></td>
</tr>
<tr>
<td><strong>Serum LDH level</strong></td>
</tr>
<tr>
<td><strong>Number of nodal sites</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk group according to FLIPI chart</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of factors</strong></td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Intermediate</td>
</tr>
<tr>
<td>High</td>
</tr>
</tbody>
</table>

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<sup>a</sup>This provides useful prognostic information which may be used to guide therapeutic decisions.


<sup>d</sup>The map is used to determine number of nodal sites in FLIPI-1 criteria and is different than the conventional Ann Arbor site map.
SUGGESTED TREATMENT REGIMENS<sup>a,b</sup>
(in alphabetical order)

**First-Line Therapy<sup>c,d</sup>**
- Bendamustine + rituximab (category 1)
- R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)
- RCVP (rituximab, cyclophosphamide, vincristine, prednisone) (category 1)
- Fludarabine + rituximab
- RFND (rituximab, fludarabine, mitoxantrone, dexamethasone)
- Radioimmunotherapy<sup>e,f</sup> (category 2B)
- Rituximab

**First-Line Therapy for Elderly or Infirm**
(if none of the above are tolerable)
- Radioimmunotherapy
- Rituximab, preferred
- Single-agent alkylators ± rituximab (e.g., chlorambucil or cyclophosphamide)

**First-Line Consolidation or Extended Dosing**
- Chemotherapy followed by radioimmunotherapy<sup>e,f,g</sup> (category 1)
- Rituximab maintenance<sup>h</sup> up to 2 y (category 1)

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

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<sup>a</sup>See references for regimens, page 504.
<sup>b</sup>The choice of initial therapy requires consideration of many factors, including age, comorbidities, and future treatment possibilities (e.g., HDT with SCR). Therefore, treatment selection is highly individualized.
<sup>c</sup>In combination chemotherapy, addition of rituximab has consistently increased overall response rate, response duration, and progression-free survival. In addition, some studies have demonstrated an overall survival benefit.
<sup>d</sup>Initial management of patients with follicular lymphoma should include rituximab; use caution in patients with hepatitis B.
<sup>e</sup>Selection of patients requires adequate marrow cellularity > 15% and < 25% involvement of lymphoma in bone marrow, and platelets > 100,000. In patients with prior autologous stem cell rescue, referral to a tertiary care center is highly recommended for radioimmunotherapy.

<sup>f</sup>If radioimmunotherapy is considered, bilateral cores are recommended and the pathologist should provide the percent of overall cellular elements and the percent of cellular elements involved in the marrow. Cytogenetics ± FISH for known MDS markers. Updates as of 2010 suggest a trend towards an increased risk of MDS with RIT treatment.
*The full impact of an induction regimen containing rituximab on RIT consolidation is unknown.
<sup>g</sup>High-dose therapy with autologous stem cell rescue is an appropriate consolidative therapy to patients in second or third remission.
<sup>h</sup>In highly selected patients, trials of fully ablative and nonmyeloablative autologous stem cell transplant have shown long term survival advantage, although there is a 2-year treatment-related mortality rate of approximately 25% for nonmyeloablative and 40% for fully ablative.
FOLLICULAR LYMPHOMA (GRADE 1–2)


SUGGESTED TREATMENT REGIMENS

References

First-Line Therapy

Bendamustine + Rituximab:
Richters J, Niemeyer C, Hainsworth JD, et al. Bendamustine plus rituximab is superior in respect of progression-free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: final results of a randomized phase III study of the STIL (Study Group Indolent Lymphomas, Germany) [abstract]. Blood 2009;114:Abstract 405.

Cyclophosphamide

CHOP (Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone) + Rituximab


CVP (Cyclophosphamide, Vincristine, and Prednisone) + Rituximab

Fludarabine + Rituximab

FND (Fludarabine, Mitoxantrone, and Dexamethasone) + Rituximab

Chemotherapy followed by rituximab

Second-Line Therapy

Bendamustine


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

Radioimmunotherapy


Second-Line Extended Dosing

Rituximab maintenance


DIFFUSE LARGE B-CELL LYMPHOMA

DIAGNOSIS*a,b

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

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- Additional immunohistochemical studies to establish lymphoma subtype
  - Paraffin panel: cyclin D1, kappa/lambda, CD138, EBV, ALK, HTLV
- Molecular genetic analysis to detect: antigen receptor gene rearrangements; BCL1, BCL2, MYC rearrangements*f
- Cytogenetics or FISH: t(14;18);*e t(3;v); t(8;14)

SUBTYPES

- Subtypes included:
  - Diffuse large B-cell lymphoma (DLBCL), NOSf
  - DLBCL coexistent with follicular lymphoma of any grade
  - DLBCL coexistent with gastric MALT lymphoma
  - DLBCL coexistent with nongastric MALT lymphoma
  - Follicular lymphoma grade 3
  - Intravascular large B-cell lymphoma
  - DLBCL associated with chronic inflammation
  - ALK-positive DLBCL
  - EBV-positive DLBCL of the elderly
  - T-cell/histiocyte-rich large B-cell lymphoma

- Subtypes not included:
  - Cutaneous B-cell lymphoma (see page 513)
  - Primary DLBCL of the CNS

Primary Mediastinal Large B-Cell Lymphoma (PMBL), page 510.

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*aBurkitt lymphoma intermediate histology or DLBCL CD10 + tumors with very high proliferation > 90% with or without Burkitt lymphoma-like features might be considered for more aggressive treatment, as shown in these guidelines, online, at www.NCCN.org [BURK-A].
bSee International Prognostic Index (page 510).
cTypical immunophenotype: CD20+, CD45+, CD3-; other markers used for subclassification.
dSee Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms (available online, in these guidelines, at www.NCCN.org [NHODG-A]).
eStandard of care is not established for DLBCL with t(14;18) with concurrent MYC rearrangements.
fGerminai center (or follicular center) cell phenotype is not equivalent to follicular lymphoma and can occur in DLBCL and Burkitt lymphoma. Morphology is required to establish diagnosis.
DIFFUSE LARGE B-CELL LYMPHOMA

WORKUP

**ESSENTIAL:**
- Physical exam: attention to node-bearing areas, including Waldeyer’s ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC, differential, platelets
- LDH
- Comprehensive metabolic panel
- Uric acid
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Unilateral or bilateral bone marrow biopsy (1-2 cm ± aspirate)
- Calculation of International Prognostic Index (IPI)
- Hepatitis B testing
- MUGA scan/echocardiogram if anthracycline or anthracyclines-based regimen is indicated
- PET-CT scan
- Pregnancy testing in women of child-bearing age
- Beta-2-microglobulin (category 2B)

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

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STAGE

**Stage I, II**
- Adverse risk factors present:
  - Elevated LDH
  - Stage II
  - Age > 60 y
  - Performance status ≥ 2
- R-CHOP x 3 cycles + RT
- R-CHOP x 6 cycles ± RT

**Stage III, IV**
- Adverse risk factors not present
- R-CHOP x 3 cycles + RT
- R-CHOP x 6 cycles ± RT

**Bulky (≥ 10 cm)**
- R-CHOP x 6 cycles ± RT

**Nonbulky (< 10 cm)**
- R-CHOP x 6 cycles + RT

---

INDUCTION THERAPY

**Consider prophylaxis for tumor lysis syndrome (available online, in these guidelines, at www.NCCN.org [NHODG-B])**

**R-CHOP x 3 cycles + RT**
- or
- R-CHOP x 6 cycles ± RT

**R-CHOP x 3 cycles + RT**
- or
- R-CHOP x 6 cycles ± RT

**R-CHOP x 6 cycles ± RT**
- or
- R-CHOP x 6 cycles + RT

**Clinical trial**
- or
- R-CHOP x 6 cycles (category 1)

**See Interim Restaging (page 508)**

---

Recent data regarding stage IE DLBCL of breast has been suggested as a potential risk for CNS disease.

Recommendations are for HIV-negative lymphoma only. For HIV-positive DLBCL, see page AIDS-2 in these guidelines, online, at www.NCCN.org.

See Principles of Radiation Therapy (available online, in these guidelines, at www.NCCN.org [NHODG-E]).

May include high-dose therapy.

Based on current clinical trials, CHOP is preferable because of reduced toxicities, but other comparable anthracycline-based regimens are acceptable.

For other regimens, see pages 511 and 512.

In selected cases, RT to initially bulky sites of disease may be beneficial (category 2B).
In patients who are not candidates for chemotherapy involved field radiation therapy (IFRT) is recommended. In selected settings (paranasal sinus, testicular, epidural, bone marrow with large cell lymphoma, HIV lymphoma, or 2 extranodal sites), radiation therapy (IFRT) is recommended. For other regimens, see pages 511 and 512. Based on current clinical trials, CHOP is preferable because of reduced toxicities, but other comparable anthracycline-based regimens are acceptable.

Recent data regarding stage IE DLBCL of breast has been suggested as a potential risk for CNS disease. CNS prophylaxis should be given (4-8 doses of intrathecal methotrexate and/or cytarabine during the course of treatment).

Stage III, IV

- pre-RT evaluation, repeat all positive studies. If PET-CT scan positive, rebiopsy before changing course of treatment

- Stage I, II: complete planned course of treatment

- Partial response (PET-positive)

- Partial response (PET-positive)

- No response or progressive disease

- See Additional Therapy for Relapse (page 509)

- Complete planned course of treatment

- Complete course of therapy with higher RT dose (category 1) or High-dose therapy with autologous stem cell rescue ± RT pre- or posttransplant or Clinical trial (may include allogeneic stem cell transplant ± RT pre- or posttransplant)

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

- Complete response

- Partial response

- No response or progressive disease

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

1 See Principles of Radiation Therapy (available online, in these guidelines, at www.NCCN.org [NHODG-E]).

2 See Response Criteria for Lymphomas (available online, in these guidelines, at www.NCCN.org [NHODG-C]).

3 Documented PR includes a biological measure of disease: positive PET-CT scan, or ideally positive biopsy. A wait a minimum of 8 weeks after RT to repeat PET-CT scan. The optimum timing of repeat PET-CT is unknown. False-positives may occur from posttreatment changes.

4 Evidence shows that addition of maintenance rituximab does not improve survival.

5 Patients in first remission may be candidates for consolidation trials, including high-dose therapy with autologous stem cell rescue.

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

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

Stage III, IV: after 2-4 cycles, repeat all positive studies

INTERIM RESTAGING

FOLLOW-UP THERAPY

END OF TREATMENT RESTAGING

INITIAL RESPONSE

(after completion of induction chemotherapy)

Complete response (PET-negative)

Partial response (PET-positive)

No response or progressive disease

See Additional Therapy for Relapse (page 509) or RT in select patients who are not candidates for chemotherapy

Complete response

Partial response (PET-positive)

No response or progressive disease

Complete response

Partial response (PET-negative)

Observation (preferred) or Consider RT to initially bulky disease (category 2B) or Consider high-dose therapy with autologous stem cell rescue in high-risk patients (category 2B)

Continue R-CHOP to a total of 6 cycles

Continue R-CHOP to a total of 6 cycles or Clinical trial

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

Partial response (PET-positive)

No response or progressive disease

Clinical trials or individual regimens: patients who progress after 3 successive regimens are unlikely to derive additional benefit from currently used combination chemotherapy regimens, except for patients with a long disease-free interval.

See Response Criteria for Lymphoma (available online, in these guidelines, at www.NCCN.org [NHODG-C]).

Additional RT can be given before or after high-dose therapy with stem cell rescue to sites of previous positive disease. Selected cases include mobilization failures and persistent bone marrow involvement.

Evidence shows that the addition of maintenance rituximab does not improve survival.

Patients in first remission may be candidates for consolidation trials, including high-dose therapy with autologous stem cell rescue.

PET-CT scan at interim restaging can lead to increased false-positives and should be carefully considered in select cases. If PET-CT scan performed and positive, rebiopsy before changing course of treatment.

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

For other regimens, see pages 511 and 512.

For other regimens, see pages 511 and 512.

For other regimens, see pages 511 and 512.

For other regimens, see pages 511 and 512.

For other regimens, see pages 511 and 512.

For other regimens, see pages 511 and 512.

For other regimens, see pages 511 and 512.

### DIFFUSE LARGE B-CELL LYMPHOMA

#### RELAPSE/REFRACTORY DISEASE

- **For patients with intention to proceed to high-dose therapy**
  - **ADDITIONAL THERAPY**
    - Second-line therapy
    - See Suggested Regimens (pages 511 and 512)
  - **RESPONSE #2**
    - Complete response or partial response

- **Relapse/ refractory disease**
  - **ADDITIONAL THERAPY**
    - Clinical trial
    - Second-line therapy
    - See Suggested Regimens (pages 511 and 512)
  - **RESPONSE #2**
    - No response

- **Non-candidates for high-dose therapy**
  - **ADDITIONAL THERAPY**
    - Clinical trial
    - Second-line therapy
    - See Suggested Regimens (pages 511 and 512)
    - Palliative RT

#### CONSOLIDATION/ADDITIONAL THERAPY

- **RESPONSE #2**
  - High-dose therapy with autologous stem cell rescue (category 1 for CR, category 2A for all others) ± involved-field RT
  - Clinical trial
  - Allogeneic stem cell transplant in selected cases

#### RELAPSE #2 OR GREATER

- Clinical trial
- Clinical trial or Palliative RT or Best supportive care

---

*See Response Criteria for Lymphoma (available online, in these guidelines, at www.NCCN.org [NHODG-C]).

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

*Selected cases include mobilization failures and persistent bone marrow involvement.

*Clinical trials or individual regimens: patients who progress after 3 successive regimens are unlikely to derive additional benefit from currently used combination chemotherapy regimens, except for patients with a long disease-free interval.
**Non-Hodgkin’s Lymphomas Version 2:2011**

**INTERNATIONAL PROGNOSTIC INDEX**

<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 2</td>
</tr>
<tr>
<td>Performance status 2-4</td>
<td>High intermediate 3</td>
</tr>
<tr>
<td>Stage III or IV</td>
<td>High 4 or 5</td>
</tr>
<tr>
<td>Extranodal involvement &gt; 1 site</td>
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</table>

**AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX**

<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 1</td>
</tr>
<tr>
<td>Performance status 2-4</td>
<td>High/intermediate 2</td>
</tr>
<tr>
<td></td>
<td>High 3</td>
</tr>
</tbody>
</table>


**Primary Mediastinal Large B-Cell Lymphoma (PMBL)**

PMBL can be defined as a clinical entity presenting with primary site of disease in mediastinum with or without other sites and has histology of DLBCL.

- Clinical pathologic correlation is required to establish diagnosis.
- Optimal first-line therapy is more controversial than other subtypes of NHL.
- Because of relative rarity of PMBL, the role of R-CHOP-21 is not established as the definitive treatment option for this disease. However, R-CHOP-21 is widely used in NCCN Member Institutions based on data in DLBCL, and other regimens have been used (see pages 511 and 512). Data suggest that more intense therapy may be better based on nonrandomized comparisons.
- Role of RT is controversial; if PET-CT scan negative at the end of treatment, may be observed.
- Residual mediastinal masses are common. PET-CT scan is essential posttreatment. Biopsy of PET-CT scan positive mass is recommended if additional treatment is contemplated.

DIFFUSE LARGE B-CELL LYMPHOMA

SUGGESTED TREATMENT REGIMENS
(in alphabetical order)

First-Line Therapy
- R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)
- Dose-dense R-CHOP-14 (category 2B)
- Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab (category 2B)

First-Line Therapy for Patients With Poor Left Ventricular Function
- RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine)
- RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, prednisone)
- RCNOP (rituximab, cyclophosphamide, mitoxantrone, vincristine, prednisone)
- DA-EPOCHR (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab
- RCEOP (rituximab, cyclophosphamide, etoposide, vincristine, prednisone)

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

Second-Line Therapy
- DHAP (dexamethasone, cisplatin, cytarabine) ± rituximab
- ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± rituximab
- GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab
- GemOx (gemcitabine, oxaliplatin) ± rituximab
- ICE (ifosfamide, carboplatin, etoposide) ± rituximab
- MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± rituximab

Second-Line Therapy (noncandidates for high-dose therapy)
- Clinical trial
- CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) ± rituximab - PO and IV
- DA-EPOCH ± rituximab
- CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± rituximab
- GDP ± rituximab
- GemOx ± rituximab
- Lenalidomide ± rituximab
- Rituximab

See references for regimens page 512.

Inclusion of any anthracycline or anthracenedione in patients with impaired cardiac function should have more frequent cardiac monitoring.

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

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

Additional anthracycline is administered after a full course of therapy, careful cardiac monitoring is essential. Dexrazoxane may be added as a cardioprotectant.

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

ESSENTIAL:
- Review of all slides with at least one paraffin block representative of the tumor should be done by a pathologist with expertise in the diagnosis of primary cutaneous B-cell lymphoma. Rebiopsy if consult material is nondiagnostic
- Histopathology review of adequate biopsy (punch, incisional, excisional)
- Adequate immunophenotyping to establish diagnosis
  - Recommended panel for paraffin section immunohistochemistry: CD20, CD79a, CD3, CD5, CD10, BCL2, BCL6, Ki-67, kappa/lambda, IRF4/MUM1

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

NOTE: A germinal (or follicle) center phenotype and large cells in a skin lesion is not equivalent to DLBCL but is consistent with primary cutaneous germinal/follicle center lymphoma.

ESSENTIAL:
- Complete history and physical examination, including complete skin exam
- CBC, differential, comprehensive metabolic panel
- LDH
- Hepatitis B testing if rituximab considered
- Chest/abdominal/pelvic CT
- Bone marrow biopsy, if PC-DLBLCL, leg-type
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

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

See Initial Therapy for Primary Cutaneous Marginal Zone Lymphoma (page 514)

See Initial Therapy for Primary Cutaneous Follicle Center B-Cell Lymphoma (page 514)

See Initial Therapy for Primary Cutaneous B-Cell Lymphoma, Leg-Type (page 516)

PC-DLBLCL, leg-type: Primary cutaneous diffuse large B-cell lymphoma, leg-type
PCMZL: Primary cutaneous marginal zone B-cell lymphoma
PCFCL: Primary cutaneous follicle center B-cell lymphoma

For noncutaneous, see Nongastric MALT Lymphoma (available online, in these guidelines, at www.NCCN.org [NGMLT-1]).

See Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms (available online, in these guidelines, at www.NCCN.org [NHODG-A]).

Typical immunophenotype: PC-DLBLCL: CD20+, Bcl2+, Bcl6+/-, IRF4/MUM1+/-; PCFCL: CD20+, Bcl2-, Bcl6+, IRF4/MUM1-; PCMZL: CD20+, Bcl2+, CD10-, Bcl6+, IRF4/MUM1+; cytoplasmic kappa+ or lambda+ in approximately 40%

Rule out drug-induced cutaneous lymphoid hyperplasia.

Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.
Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

**PRIMARY CUTANEOUS MARGINAL ZONE OR FOLLICLE CENTER B-CELL LYMPHOMA**

**RELAPSED DISEASE**

**STAGE**

- **Solitary/regional, T1-2** (Ann Arbor stage IE)
  - Observation or Excision or Topicals or Local RT
  - CR/PR → Persistent or progressive disease
  - Refractory

- **Generalized disease** (skin only), T3
  - Observation or Rituximab or Topicals or Intralvesional steroids or Local RT
  - CR/PR → Persistent or progressive disease
  - Refractory

- **Extracutaneous disease**
  - Manage as per page 499

**ADDITIONAL THERAPY**

- **Regional**
  - Generalized disease (extracutaneous disease)
  - Manage as per page 499

- **Generalized disease** (skin only)

- **Relapsed**

- **Observed**
  - Observation or Excision or Topicals or Local RT
  - CR/PR → Persistent or progressive disease
  - Refractory

- **Persisted or progressed**
  - Observation or Rituximab or Topicals or Local RT
  - CR/PR → Persistent or progressive disease
  - Refractory

See Monoclonal Antibody Directed at CD20 and Viral Reactivation (available online, in these guidelines, at www.NCCN.org [NHODG-D])

---

1. Unless clinically indicated, additional imaging studies during the course of treatment is not needed.
2. See TNM Classification of Cutaneous Lymphoma other than MF/SS (pages 517 and 518).
3. See Treatment References (page 519).
4. There are case reports showing efficacy of topicals which include steroids, imiquimod, nitrogen mustard, and bexarotene.
5. In rare circumstances for very extensive disease, other combination chemotherapy regimens listed on page 503 are used.
6. Refractory to all previous treatments.
### PRIMARY CUTANEOUS DIFFUSE LARGE B-CELL LYMPHOMA, LEG TYPE

<table>
<thead>
<tr>
<th>STAGE</th>
<th>INITIAL THERAPY</th>
<th>SECONDARY THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solitary regional, T1-2 (Ann Arbor stage IE)</td>
<td>R-CHOP(^m) + local RT or Local RT(^n) or Clinical trial</td>
<td>CR → Observe → Relapse → R-CHOP (if not previously received) or Manage as per page 509 or Local RT to previously unirradiated tumor</td>
</tr>
<tr>
<td>Generalized disease (skin only), T3</td>
<td>R-CHOP ± local RT or Clinical trial</td>
<td>CR → Observe → Relapse → Manage as per page 509 or Local RT for palliation or Radioimmunotherapy</td>
</tr>
<tr>
<td>Extracutaneous disease</td>
<td>Manage as per page 506</td>
<td></td>
</tr>
</tbody>
</table>

### TNM CLASSIFICATION OF CUTANEOUS LYMPHOMA OTHER THAN MF/SS

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>a solitary lesion &lt; 5 cm diameter</td>
</tr>
<tr>
<td>T1b</td>
<td>a solitary &gt; 5 cm diameter</td>
</tr>
<tr>
<td>T2a</td>
<td>all-disease-encompassing in a &lt; 15-cm-diameter circular area</td>
</tr>
<tr>
<td>T2b</td>
<td>all-disease-encompassing in a &gt; 15- and &lt; 30-cm-diameter circular area</td>
</tr>
<tr>
<td>T2c</td>
<td>all-disease-encompassing in a &gt; 30-cm-diameter circular area</td>
</tr>
<tr>
<td>T3a</td>
<td>multiple lesions involving 2 noncontiguous body regions</td>
</tr>
<tr>
<td>T3b</td>
<td>multiple lesions involving 3 body regions</td>
</tr>
<tr>
<td>T4</td>
<td>multiple lesions involving &gt; 3 body regions</td>
</tr>
</tbody>
</table>

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

| M0    | No evidence of extracutaneous non–lymph node disease |
| M1    | Extracutaneous non lymph node disease present |

See Monoclonal Antibody Directed at CD20 and Viral Reactivation (available online, in these guidelines, at www.NCCN.org [NHODG-D]).

---

\(^9\)See TNM Classification of Cutaneous Lymphoma other than MF/SS (pages 517 and 518).

\(^m\)For alternate regimens, see page 511.

\(^n\)For patients not able to tolerate chemotherapy.

Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.
### Non-Hodgkin’s Lymphomas Version 2:2011  PRIMARY CUTANEOUS B-CELL LYMPHOMA

#### TNM CLASSIFICATION OF CUTANEOUS LYMPHOMA OTHER THAN MF/SS

<table>
<thead>
<tr>
<th>T</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Solitary skin involvement</td>
</tr>
<tr>
<td>T1a</td>
<td>a solitary lesion &lt; 5 cm diameter</td>
</tr>
<tr>
<td>T1b</td>
<td>a solitary &gt; 5 cm diameter</td>
</tr>
<tr>
<td>T2</td>
<td>Regional skin involvement: multiple lesions limited to 1 body region or 2 contiguous body regions</td>
</tr>
<tr>
<td>T2a</td>
<td>all-disease-encompassing in a &lt; 15-cm-diameter circular area</td>
</tr>
<tr>
<td>T2b</td>
<td>all-disease-encompassing in a &gt; 15- and &lt; 30-cm-diameter circular area</td>
</tr>
<tr>
<td>T2c</td>
<td>all-disease-encompassing in a &gt; 30-cm-diameter circular area</td>
</tr>
<tr>
<td>T3</td>
<td>Generalized skin involvement</td>
</tr>
<tr>
<td>T3a</td>
<td>multiple lesions involving 2 noncontiguous body regions</td>
</tr>
<tr>
<td>T3b</td>
<td>multiple lesions involving ≥ 3 body regions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>No clinical or pathologic lymph node involvement</td>
</tr>
<tr>
<td>N1</td>
<td>Involvement of 1 peripheral lymph node region that drains an area of current or prior skin involvement</td>
</tr>
<tr>
<td>N2</td>
<td>Involvement of 2 or more peripheral lymph node regions or involvement of any lymph node region that does not drain an area of current or prior skin involvement</td>
</tr>
<tr>
<td>N3</td>
<td>Involvement of central lymph nodes</td>
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</table>

<table>
<thead>
<tr>
<th>M</th>
<th>Description</th>
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<tbody>
<tr>
<td>M0</td>
<td>No evidence of extracutaneous non-lymph node disease</td>
</tr>
<tr>
<td>M1</td>
<td>Extracutaneous non-lymph node disease present</td>
</tr>
</tbody>
</table>

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**Note:**

- This work was originally published in Blood. Kim YH, Willemze R, Pimpinell Ni, et al, for the ISCL and the EORTC. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC) Blood 2007;110:479-484. © the American Society of Hematology.
- For definition of body regions, see Body Regions for the Designation of T (skin involvement) Category (page 518).
- Definition of lymph node regions is consistent with the Ann Arbor system: Peripheral sites: antecubital, cervical, supraclavicular, axillary, inguinal-femoral, and popliteal. Central sites: mediastinal, pulmonary hilar, paraortic, iliac.
**BODY REGIONS FOR THE DESIGNATION OF T (SKIN INVOLVEMENT) CATEGORY**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HN</td>
<td>Head &amp; Neck</td>
</tr>
<tr>
<td>C</td>
<td>Chest</td>
</tr>
<tr>
<td>LUA</td>
<td>Left Upper Arm</td>
</tr>
<tr>
<td>LLAH</td>
<td>Left Lower Arm &amp; Hand</td>
</tr>
<tr>
<td>AG</td>
<td>Abdominal &amp; Genital</td>
</tr>
<tr>
<td>LUL</td>
<td>Left Upper Leg</td>
</tr>
<tr>
<td>LLLF</td>
<td>Left Lower Leg &amp; Feet</td>
</tr>
<tr>
<td>RUA</td>
<td>Right Upper Arm</td>
</tr>
<tr>
<td>RLAH</td>
<td>Right Lower Arm &amp; Hand</td>
</tr>
<tr>
<td>RUL</td>
<td>Right Upper Leg</td>
</tr>
<tr>
<td>RLLF</td>
<td>Right Lower Leg &amp; Feet</td>
</tr>
<tr>
<td>UB</td>
<td>Upper Back</td>
</tr>
<tr>
<td>LBB</td>
<td>Lower Back &amp; Buttock</td>
</tr>
</tbody>
</table>

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**Footnotes:**


- bLeft and right extremities are assessed as separate body regions. The designation of these body regions is based on regional lymph node drainage patterns.


The designation of these body regions are based on regional lymph node drainage patterns.

**TREATMENT REFERENCES**

**Rituximab**


**Topicals**

Topical/intralesional corticosteroids

Topical nitrogen mustard

Topical bexarotene

Topical imiquimod


**Chemotherapy**


IWF Classification
The IWF classified NHL as either low-, intermediate-, or high-grade based on the morphology and natural history. This classification divided diffuse large B-cell lymphoma (DLBCL) into intermediate- and high-grade groups. However, these distinctions were not reproducible. Because this classification did not include immunophenotyping, the categories were not reproducible. In addition, after this classification was published, many new diseases were described that were not included in the IWF classification.

Revised European-American Lymphoma Classification
In 1994, the International Lymphoma Study Group developed the Revised European-American Lymphoma (REAL) classification, which classified lymphomas based on the cell of origin (B, T, or NK) and included morphology, immunophenotype, genetic, and clinical features to define diseases. In 1997, the International Lymphoma Classification Project performed a clinical evaluation of the REAL classification in a cohort of 1403 cases of NHL confirming the diagnosis of NHL in 1378 (98.2%). This study identified the 13 most common histologic types, constituting approximately 90% of the cases of NHL in the United States. The findings were as follows: DLBCL, 31%; follicular lymphoma (FL), 22%; small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL), 6%; mantle cell lymphoma (MCL), 6%; peripheral T-cell lymphoma (PTCL), 6%; and mucosa-associated lymphoid tissue (MALT) lymphoma, 5%. The remaining subtypes each occurred in fewer than 2% of cases. Importantly, in the United States more than 50% of lymphoma cases are either DLBCL or FL. The study investigators concluded that the REAL classification can be readily applied and identifies clinically distinctive types of NHL.

WHO Classification
In 2001, the WHO updated the classification of hematopoietic and lymphoid neoplasms to apply the principles of the REAL classification, representing the first international consensus on classification of hematologic malignancies. The REAL/WHO classification of NHL includes many entities not recognized by the IWF. After consideration of cell of origin (B, T, or NK), the classification subdivides lymphomas into those from precursor lymphocytes versus those derived from mature lymphocytes. The classification is further refined based on immunophenotype and genetic and clinical features. These considerations have helped define active treatment for specific subtypes of lymphoma.

In 2008, the International T-Cell Lymphoma Project evaluated the WHO classification of T-cell lymphoma in a cohort of 1314 cases of PTCL and NK/T-cell lymphomas (NKTCL). The diagnosis of PTCL or NKTCL was confirmed in 1153 cases (88%). The most common subtypes were PTCL-not otherwise specified (PTCL-NOS; 25.9%); angioimmunoblastic lymphoma (18.5%); NKTCL (10.4%); adult T-cell leukemia/lymphoma (9.6%); anaplastic large cell lymphoma (ALCL); anaplastic lymphoma kinase (ALK)-positive (6.6%); and ALCL, ALK-negative (5.5%). The findings of this study validated the efficacy of the WHO classification for defining subtypes of T-cell lymphomas. The WHO classification was updated again in September 2008 to add new diseases and subtypes that have been recognized in the past decade, and to better define some of the heterogeneous and ambiguous categories based on recent advances (available online, in these guidelines, at www.NCCN.org [ST-1]).

Response Criteria
In 1999, the IWG published guidelines for response criteria for lymphoma based on the reduction in size of the enlarged lymph node as measured by CT scan and the extent of bone marrow involvement determined through bone marrow aspirate and biopsy. These guidelines were revised in 2007 by the International Harmonization Project to incorporate immunohistochemistry, flow cytometry, and 18-fluorodeoxyglucose (FDG)–PET scans in the definition of response. In the revised guidelines, the complete response, unconfirmed category was essentially eliminated because residual masses were defined as a partial or complete response based on the result of a PET scan. Using the revised system, response is categorized as complete response, partial response, stable disease, and relapsed disease or progressive disease. However, the application of PET to responses is limited to histologies that show reliable FDG uptake in active tumor. However, the revised response criteria have thus far only been validated for DLBCL and Hodgkin lymphoma. The application of the revised response criteria to other histologies requires validation, and the original IWG guidelines should be used.
Diagnosis

Genetic features, detected using cytogenetics or fluorescence in situ hybridization (FISH), are increasingly important in defining specific NHL subtypes. In addition, detection of viruses, particularly Epstein-Barr virus (EBV), human herpesvirus 8, and human T-cell leukemia virus type 1, is often necessary to establish a specific diagnosis. In all cases, the most important first step is to make an accurate pathologic diagnosis. The basic pathologic evaluation is the same in each guideline, although some further evaluation may be useful in certain circumstances to clarify a particular diagnosis; these are outlined in the pathologic evaluation of the individual guideline.

An incisional or excisional lymph node biopsy is recommended to establish the diagnosis of NHL. Core needle biopsy is discouraged unless the clinical situation dictates that this is the only safe means of obtaining diagnostic tissue. Fine needle aspiration (FNA) biopsy is widely used in the diagnosis of malignant neoplasms, but its role in diagnosing lymphoma is still controversial.20,21 Because the revised REAL/WHO classification is based on both morphology and immunophenotyping, FNA alone is not acceptable as a reliable diagnostic tool for NHL. However, its use in combination with ancillary techniques may provide precise diagnosis, thereby obviating the need for a more invasive biopsy in highly selected circumstances. Recent studies have shown that the diagnostic accuracy of FNA improves significantly when it is used in combination with immunohistochemistry and flow cytometry.22–24

In the NCCN Guidelines, FNA results alone are not suitable for making an initial diagnosis of NHL, although it may be sufficient to establish relapse. However, in certain circumstances, when a lymph node is not easily accessible, a combination of core biopsy and FNA in conjunction with appropriate ancillary techniques (polymerase chain reaction [PCR] for IGHV and/or T-cell receptor [TCR] gene rearrangements; FISH for major translocations; immunophenotypic analysis) may be sufficient for diagnosis. This is particularly true for the diagnosis of CLL. In other entities presenting in leukemic phase, such as FL or MCL, a biopsy is still preferred to clarify histologic subtype.

Immunophenotypic analysis is essential for differentiating the various subtypes of NHL to establish the proper diagnosis. It can be performed using flow cytometry and/or immunohistochemistry; the choice depends on the antigens and the expertise and resources available to the hematopathologist. In some cases, flow cytometry and immunohistochemistry are complementary diagnostic tools.25 Cytogenetic or molecular genetic analysis may be necessary under certain circumstances to identify the specific chromosomal translocations that are characteristic of some NHL subtypes or to establish clonality.

After publication of the 2008 WHO classification, the panel developed a series of algorithms for using immunophenotyping to diagnose mature lymphoid neoplasms. These algorithms should be used in conjunction with clinical and pathologic correlation. They were developed as a guide for surgical pathologists and to help clinicians interpret pathology reports.

Initial assessment begins with morphologic, clinical, and immunophenotypic analysis. Morphologic assessment involves determining the cell size (small, medium-sized, or large cells), with or without anaplastic morphology. Clinical features include patient’s age and the location (nodal, extranodal, and, among extranodal site, skin vs. other specific sites). The initial immunophenotyping panel should include Pan-B and Pan-T-cell antigens. Based on the morphologic and clinical features, some of the B- and T-cell subset antigens may also be added in the initial panel (see Immunophenotyping and Genetic Testing in the Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms, available online, in these guidelines, at www.NCCN.org [NHODG-A]).

Workup

Essential workup procedures include a complete physical examination, with particular attention to node-bearing areas; determination of the size of liver and spleen, symptoms present, and performance status; and laboratory studies, including CBC, serum lactate dehydrogenase (LDH), hepatitis B testing (see later discussion), comprehensive metabolic panel, and CT chest/abdominal/pelvic with oral and intravenous contrast (unless coexistent renal insufficiency). Multiple-gated acquisition (MUGA) scan or echocardiograms are recommended when anthracyclines and anthracycline-containing regimens are used. Bone marrow biopsy with or without aspirate is essential whenever treatment is considered; however, it may be deferred in certain circumstances (see later discussion).
Because of the risk of hepatitis B reactivation, the panel included hepatitis B testing (hepatitis B surface antigen [HBsAg] and hepatitis B core antibody [HbcAb]) as part of essential workup in all patients before initiating anti-CD20 monoclonal antibody-based regimens. Furthermore, hepatitis B reactivation has been reported with chemotherapy alone, and therefore testing should be considered in anyone with a risk factor (e.g., blood transfusion, intravenous drug abuse) or from a region with a nonnegligible prevalence of hepatitis B infection. Further discussion is provided in Hepatitis B Virus Reactivation on the facing page. Hepatitis C testing is needed in high-risk patients and patients with splenic marginal zone lymphoma (MZL).

Optional procedures (depending on specific lymphoma type) include β₂-microglobulin, CT or PET-CT scans, endoscopic ultrasound (gastric MALT lymphoma), head CT or brain MRI, and lumbar puncture to analyze cerebrospinal fluid (MCL and DLBCL). Discussion of fertility issues and sperm banking should be addressed when appropriate.26

Bone marrow biopsy is usually included in the workup for all patients with NHL, except those with SLL/CLL in whom a clonal lymphocytosis is identified with flow cytometry. Bone marrow involvement occurs in 39% of low-grade, 36% of intermediate-grade, and 18% of high-grade lymphomas. Bone marrow involvement was associated with significantly shorter survivals in patients with intermediate- or high-grade lymphomas.27 A recent retrospective analysis analyzing the incidence of involvement and parameters predicting bone marrow involvement in 192 patients with stage I and II DLBCL found the overall incidence of bone marrow involvement to be 3.6%. The authors concluded that bone marrow biopsy may be safely omitted in selected patients with early-stage DLBCL.28 In cutaneous B-cell lymphomas, bone marrow biopsy is essential for primary cutaneous DLBCL, leg-type (PCDLBCL-LT) because it is an aggressive lymphoma that will probably require systemic treatment, whereas the role of bone marrow biopsy in primary cutaneous follicle center lymphoma (PCFCL) and primary cutaneous MZL is less clear. Recent studies indicate that bone marrow biopsy is an essential component of staging in patients with PCFCL first presenting in the skin, whereas it seems to have limited value in patients with MZL presenting in the skin, and may be considered only in selected cases.29,30

In these guidelines, bone marrow biopsy with or without aspirate is included as part of the essential workup for all lymphomas. However, in patients with low-bulk indolent disease with radiographic clinical stage III disease, an initial staging bone marrow evaluation can be deferred if observation is recommended because it will not change the clinical recommendations. However, in the evaluation of potentially early-stage indolent lymphoma (stage I or II), bone marrow biopsy is essential; some panel members advocate bilateral core biopsies in this situation.31 Bilateral cores are recommended if radioimmunotherapy is considered.

FDG-PET scan has been used for initial staging, restaging, and follow-up of patients with NHL.32 In a recent meta-analysis, PET showed a high positivity and specificity when used to stage and restage patients with lymphoma.33 FDG-PET is nearly universally positive at diagnosis in Hodgkin lymphoma, DLBCL, and FL34; approximately 90% in T-cell lymphoma35 and nodal MZL; but less sensitive for extranodal MZL.36 However, several benign conditions, including sarcoid, infection, and inflammation, can result in false-positive PET scans complicating the interpretation. Lesions smaller than 1 cm are not reliably visualized with PET scans. PET scan is now part of the pretreatment evaluation in Hodgkin lymphoma and DLBCL, and may be useful in selected cases with other histologies. The pretreatment PET scan is particularly important in helping to interpret posttreatment response evaluation according to new response criteria (see previous discussion). At diagnosis, PET scans may detect additional disease sites, although the clinical stage is only modified in 15% to 20% of patients and the additional information provided by the scans results in a change in treatment in only 8% of patients. PET scan has generally been used in conjunction with diagnostic CT scans.

Integrated PET-CT has largely replaced dedicated CT scans in the United States. This diagnostic study has distinct advantages in both staging and restaging compared with full-dose diagnostic CT or PET alone.37,38 In a retrospective study, PET-CT performed with low-dose nonenhanced CT was found to be more sensitive and specific than routine contrast-enhanced CT in evaluating lymph node and organ involvement in patients with Hodgkin disease or high-grade NHL.39 Preliminary results of another recent prospective study (47 patients; patients who
had undergone prior diagnostic CT were excluded) showed a good correlation between low-dose unenhanced PET-CT and full-dose enhanced PET-CT in the evaluation of lymph nodes and extranodal disease in lymphomas.\textsuperscript{37} However, the lack of intravenous contrast and the diminished resolution can make the anatomic localization and significance of FDG-avid sites difficult to interpret in some cases. Further studies are needed to determine if PET-CT scans can replace diagnostic CT scans in the initial staging and response evaluation of lymphomas. The panel has included PET-CT scan as an optional workup procedure for selected patients.

### Supportive Care

#### Hepatitis B Virus Reactivation

Hepatitis B virus (HBV) reactivation has been reported to occur in patients treated with chemotherapy with or without anti-CD20 monoclonal antibody. Treatment with rituximab alone is also a risk for hepatitis B reactivation.\textsuperscript{39} HBV-reactivation may result in a fulminant hepatitis, hepatic failure, and death. The median time to hepatitis diagnosis was approximately 4 months after the initiation, according to the package insert (www.fda.gov).

Testing of patients at risk for hepatitis B reactivation should include HBsAg and HBcAb. In a prospective study of all patients undergoing immunosuppressive therapy (chemotherapy, antibody therapy, high-dose dexamethasone) at Memorial Sloan-Kettering Cancer Center, 1% of patients were HBsAg-positive and 9% were HBcAb-positive.\textsuperscript{40} A retrospective study conducted by MD Anderson Cancer Center reported similar findings (HBsAg and HBcAb were positive in 2% and 8% of patients, respectively).\textsuperscript{41} Patients positive for HBsAg are at a greater risk for HBV reactivation than those positive for HBcAb.\textsuperscript{39} In a prospective study of 100 Chinese patients undergoing chemotherapy for lymphoma, hepatitis developed in 67% of HBsAg-positive patients and 14% HBsAg-negative patients during cytotoxic therapy.\textsuperscript{42} Other risk factors for reactivation include young age, male gender, elevated pretreatment viral load, and prolonged immunosuppression.\textsuperscript{43,44} The use of rituximab in HBcAb-positive patients has been reported to cause fatal HBV-related liver disease. A retrospective study of Italian HBcAb-positive patients with lymphoma found that 2.7% of patients treated with rituximab and chemotherapy developed HBV-related liver disease compared with 0.8% of patients treated with chemotherapy alone. HBV-related liver disease was not seen in patients who were observed or underwent other therapy (radiation, antibiotics, interferon).\textsuperscript{45}

Antiviral prophylaxis has been effective in preventing hepatitis B reactivation during chemoinmunotherapy in HBsAg-positive patients.\textsuperscript{46-48} The results of a systematic review of 14 studies involving HBsAg-positive patients undergoing chemotherapy showed that lamivudine prophylaxis reduced the risk for HBV reactivation by 79% or greater; HBV-associated hepatic failure and death may also be reduced.\textsuperscript{46}

None of the patients in the preventive lamivudine group developed HBV-related hepatic failure, compared with 21 of 162 patients in the control group, and only 4 deaths were attributable to HBV in the preventive lamivudine group compared with 27 deaths in the control group. Lamivudine was well tolerated with no adverse effects. In a small randomized study, Lau et al.\textsuperscript{49} showed that preemptive antiviral treatment with lamivudine was superior to deferred treatment. This study randomized 30 patients with HBsAg-positive lymphoma to receive lamivudine either before chemotherapy or for the treatment of increased viral load based on HBV DNA PCR levels. HBV reactivation was observed in 53% of monitored patients and none in the prophylaxis group. Interestingly, clinical cancer-related outcomes were also significantly better in the prophylaxis group than the treatment group.

The guidelines recommend HBsAg and HBcAb testing for all patients receiving rituximab. For patients in whom one or both of these tests are positive, a baseline hepatitis B viral load should be determined using quantitative PCR. However, a negative baseline PCR does not preclude the possibility of activation. In patients from areas with high prevalence (Asia, Africa, Eastern Europe, and portions of South America) or regions where the prevalence of HBV is unknown, all of those undergoing immunotherapy, chemotherapy, or chemoimmunotherapy should be tested for HBsAg and HBcAb. Patients receiving intravenous immunoglobulin (IVIG) may be HBcAb-positive as a consequence of IVIG therapy. Empiric antiviral therapy on oncologic treatment is recommended for any patient who is either HBsAg-
or HBcAb-positive. During the treatment period, viral load should be monitored monthly with PCR and 3 months thereafter. Patients treated with chemotherapy alone should receive prophylaxis if they have a measurable viral load independent of the viral serology. If viral load is consistently undetectable, prophylaxis should be given to HBsAg-positive patients and may be considered in patients HBcAb-positive. If viral load fails to drop, consultation with a hepatologist is recommended. However, because of the potential emergence of resistance to lamivudine, it is not the optimal drug for prophylaxis. Several appropriate agents for viral prophylaxis are available; good choice will be driven by institutional standard or recommendation from the consultant. The optimal duration of prophylaxis remains undefined, but the panel recommends it be maintained for at least 6 months after the completion of oncologic treatment.

**Progressive Multifocal Leucoencephalopathy**

Progressive multifocal leucoencephalopathy (PML) is a serious and usually fatal central nervous system infection caused by JC polyoma virus. In a recent report of 57 cases from the Research on Adverse Drug Events and Reports project, 52 patients with lymphoproliferative disorders developed PML after treatment with rituximab and other treatments, including hematopoietic stem cell transplantation (HSCT) or chemotherapy with purine analogs or alkylating agents. Median time from last rituximab dose to PML diagnosis was 5.5 months, and median time to death after diagnosis was 2.0 months. The case-fatality rate was 90%.

PML is usually diagnosed based on PCR of cerebrospinal fluid, or sometimes brain biopsy. No effective treatment exists for PML. Patients must be carefully monitored for the development of any neurologic symptoms. Currently, no pretreatment evaluation can predict for the subsequent development of PML.

**Tumor Lysis Syndrome**

Tumor lysis syndrome (TLS) is characterized by metabolic abnormalities caused by the abrupt release of intracellular contents into the blood from cellular disintegration induced by chemotherapy. It is usually observed within 12 to 72 hours after chemotherapy initiation. Untreated TLS can induce profound metabolic changes, resulting in cardiac arrhythmias, seizures, loss of muscle control, acute renal failure, and death.

Cairo and Bishop recently classified TLS into laboratory or clinical types. Laboratory TLS is defined as a 25% increase in the levels of serum uric acid, potassium, or phosphorus or a 25% decrease in calcium levels. Clinical TLS refers to laboratory TLS with clinical toxicity that requires intervention. Clinical complications may include renal insufficiency, cardiac arrhythmia, or seizures. The 4 primary electrolyte abnormalities of TLS are hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia. Symptoms associated with TLS may include nausea and vomiting, diarrhea, seizures, shortness of breath, or cardiac arrhythmias.

TLS is best managed if it is anticipated and treatment is initiated before chemotherapy. The cornerstone of management is hydration and the control of hyperuricemia. Allopurinol should be administered before the initiation of chemotherapy. When the uric acid level remains elevated despite treatment with allopurinol, or when renal insufficiency is present, treatment with rasburicase is indicated. Electrolytes and renal function should be monitored every 6 to 8 hours with appropriate interventions for hyperphosphatemia and hyperkalemia. Careful clinical monitoring will help to preempt complications, and in many cases admission to the intensive care unit is appropriate. Cardiac monitoring or serial electrocardiogram may be beneficial to identify early electrolyte-related cardiac abnormalities. Dialysis may be necessary in cases of anuric acute renal failure.

Allopurinol is a xanthine analog and a competitive inhibitor of xanthine oxidase, thereby blocking conversion of purine metabolites to uric acid. Allopurinol will decrease uric acid production and has been shown to reduce the incidence of uric acid uropathy. Because the drug inhibits new uric acid formation rather than reduces existing uric acid, elevated levels of uric acid can take several days to normalize after initiation of treatment, thereby delaying the start of chemotherapy. Furthermore, allopurinol may lead to the accumulation of xanthine crystals in renal tubules, leading to acute obstructive uropathy. Allopurinol will also reduce clearance of 6-mercaptopurine and high-dose methotrexate.

Rasburicase is a recombinant urate oxidase that catalyzes the oxidation of uric acid to a highly soluble nontoxic metabolite that is readily excreted. It has been shown to be safe and highly effective in the prevention and treatment of chemotherapy-
induced hyperuricemia in both children and adults. The GRAAL1 (Groupe d’Etude des Lymphomes de l’Adulte Trial on Rasburicase Activity in Adult Lymphoma) study evaluated the efficacy and safety of rasburicase for the prevention and treatment of hyperuricemia in patients with NHL during induction chemotherapy. Uric acid levels decreased within 4 hours after the first injection of the drug. Creatinine levels and other metabolites were also controlled with the administration of rasburicase.

Cortes et al. recently reported the results of a prospective, randomized controlled trial that compared the efficacy of rasburicase and allopurinol in adult patients with hematologic malignancies at high or potential risk for TLS. The plasma uric acid response rate was 87% for rasburicase, 78% for rasburicase plus allopurinol, and 66% for allopurinol. Rasburicase was superior to allopurinol in the overall study population, in patients at high risk for TLS (89% vs. 68%), and in patients with baseline hyperuricemia (90% vs. 53%). The time to control serum uric acid in hyperuricemic patients was 4 hours for rasburicase and 27 hours for allopurinol. However, rasburicase can induce anaphylactic reactions. Other adverse reactions include methemoglobinemia and severe hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

The risk factors for TLS include bone marrow involvement, bulky tumors that are chemosensitive, rapidly proliferative or aggressive hematologic malignancies, an elevated leukocyte count or pretreatment LDH level, preexisting elevated uric acid, renal disease, or renal involvement of tumor. Patients diagnosed with lymphoblastic lymphoma or Burkitt lymphoma are at a higher risk for developing TLS. Occasionally, patients with bulky presentation of DLBCL and those with CLL and high white blood cell count may experience TLS at a moderately high frequency.

These guidelines recommend that allopurinol be started 2 to 3 days before chemotherapy and continued for 10 to 14 days. Rasburicase is recommended for patients with any of the following risk factors: presence of any high-risk feature; bulky disease requiring immediate therapy; inability to achieve adequate hydration; allopurinol is ineffective; or acute renal failure. One dose is adequate in most cases; repeat dosing should be individualized.

### CLL/SLL

CLL and SLL are different manifestations of the same disease and are managed in much the same way. The major difference is that in CLL a significant number of the abnormal lymphocytes are also found in the bone marrow and blood, whereas in SLL the abnormal lymphocytes are predominantly found in the lymph nodes.

Cytogenetic abnormalities that can be detected with FISH are present in approximately 80% of patients with CLL. The most common abnormality is del(13q) (55%), followed by del(11q) (18%), trisomy 12 (16%), del(17p) (7%), and del(6q) (7%). Del(13q) is associated with a favorable prognosis and the longest median survival (133 months). Del(11q) is associated with extensive lymphadenopathy, disease progression, and shorter median survival (79 months). Among patients with del(11q), those with a complete loss of ATM function might have impaired response to irradiation or cytotoxic drugs, resulting in poor clinical outcome. Alkylating agent–based chemoimmunotherapy regimens have significantly improved clinical outcomes by overcoming the adverse prognostic significance of del(11q) in previously untreated patients with CLL. Del(17p) affecting TP53 is associated with shorter treatment-free intervals, shorter median survival (32 months), and poor response to chemotherapy. Recent studies have identified TP53 mutations as an independent predictor of short survival and resistance to chemotherapy. Resistance to chemotherapy has been attributed to the presence of mutation in the remaining TP53 allele. However, the natural history of patients with del(17p) can be heterogeneous, with some patients having an indolent disease course. TP53 mutation also carries a poor prognosis regardless of the presence of del(17p) when treated with fludarabine-based chemotherapy.

The impact of these prognostic factors on the clinical outcome of patients has been examined in large prospective randomized studies. In the CALGB 9712 study, unmutated IGHV (≥ 98%), del(11q), and del(17p) were identified as independent prognostic factors for overall and progression-free survival; two other studies (E2997 and LRF CLL4) identified these features as prognostic indicators for progression-free survival. In the LRF CLL4 trial, patients with 5% to 20% of cells with del(17p) had similar response rates and survival as those without
del(17p). In contrast, those with 20% or more cells with del(17p) had a poor outcome, with a 13% response rate and median overall survival of only 11 months. The finding that del(17p) is more frequently observed in treated patients than in untreated ones (20% vs. 5%–10%) suggests that treatment-driven clonal selection occurs during therapy.

New prognostic markers such as β2-microglobulin, IGHV mutational status, CD38, and zeta-associated protein 70 (ZAP-70) have been identified. Higher β2-microglobulin was an independent adverse prognostic factor in patients treated with front-line fludarabine-based chemotherapy. Unmutated IGHV is associated with a poor prognosis irrespective of disease stage. The extent of mutation is also important, with the longest survivals observed in patients with more than 3% mutations, and slightly shorter survivals seen in those with 1% to 2% mutations. A subset of patients in whom the IGHV3-21 variable region is rearranged have more aggressive disease and shorter survival regardless of the mutation status.

Overexpression of CD38 (≥ 30%) and ZAP-70 (≥ 20%) is also associated with a poor prognosis. However, the fact that these cutoffs are based on flow cytometry and reproducibility across laboratories remains a problem. Recent studies have shown that the combined analysis of ZAP-70 and CD38 expression provides a more discriminatory prediction of treatment-free interval than each factor alone. Wierda et al. developed a nomogram using age, β2-microglobulin, absolute lymphocyte count, sex, Rai stage, and number of involved lymph nodes, which may help stratify untreated patients with CLL into 3 different risk groups (low, intermediate, and high). The estimated median survival times were not reached for low-risk groups. The median survival times for intermediate- and high-risk groups were 10 and 5 years, respectively. The 5- and 10-year overall survival rates were 97% and 80%, 80% and 52%, and 55% and 26%, respectively. This prognostic model must be validated in prospective studies.

**Staging**

The nearly universal involvement of the bone marrow and peripheral blood in CLL/SLL limits the utility of the Ann Arbor staging system. Two different staging systems, Rai and Binet, are currently used worldwide. The modified Rai classification is most useful clinically and provides important prognostic information. The survival rate of patients with low-risk disease (Rai stage 0) is essentially the same as that of age-matched controls. Patients with intermediate-risk disease (Rai stage I–II) have a shorter survival, particularly when other adverse factors coexist, such as a lymphocyte doubling time of less than 1 year. Patients with high-risk disease (Rai stage III–IV) have a poor prognosis. The Binet staging system is based on the number of involved areas and the level of hemoglobin and platelets and, like the Rai system, has a good correlation with clinical outcome.

**Diagnosis**

The diagnosis of CLL requires the presence of at least 5000 malignant B cells/mm3. The presence of fewer B cells in the absence of lymphadenopathy or other clinical features characteristic of a lymphoproliferative disorder is defined as monoclonal B lymphocytosis (MBL). MBL is a relatively recent diagnostic category consisting of individuals with an abnormal B-cell population but do not meet the diagnostic criteria for CLL. Most cases of MBL have the immunophenotype of CLL (discussed later). The “favorable” molecular lesions, mutated IGHV and del(13q), are commonly seen in patients with MBL. The estimated rate of progression of MBL to CLL requiring treatment is 1.1% per year. A CT scan is essential to distinguish MBL from CLL. The CLL/SLL guideline now includes an initial stratification between CLL/SLL and MBL (absolute lymphocyte count < 5000 B cells/mm3, lymph nodes < 1.5 cm, no anemia or thrombocytopenia). Observation is recommended for all patients diagnosed with MBL.

Adequate immunophenotyping using flow cytometry of peripheral blood or paraffin-section immunohistochemistry is required to confirm the diagnosis of CLL/SLL. The recommended panel for immunohistochemistry includes CD3, CD5, CD10, CD20, CD23, and cyclin D1. These can be useful, particularly for diagnosing CLL/SLL type without circulating cells. Cell surface markers for flow cytometric studies include kappa/lambda, CD19, CD20, CD5, CD23, and CD10. Additional paraffin-embedded material may be used for immunophenotyping to determine lineage and clonality.

The typical immunophenotype includes CD5+, CD10–, CD19+, CD20, dim expression of surface immunoglobulin, CD23+, CD43+/–, and cyclin D1–. Distinguishing CLL/SLL from MCL is essential because they are both CD5+ B-cell tumors. Although
CD23 is often helpful, cyclin D1 is critical in this differentiation of tumor types. FISH for detecting t(11;14) can help distinguish MCL from CLL. Cytogenetics and/or FISH for detecting del(11q), del(13q), trisomy 12, and del(17p), and molecular genetic analysis to detect IGHV mutation status, can provide prognostic information and guide selection of therapy. Although FISH is optional for patients with Rai low-risk disease for whom observation would be recommended, it should be evaluated any time therapy is considered. Cytogenetic abnormalities can evolve over time, and therefore reevaluation of FISH is necessary to direct treatment options in patients with indications for treatment. CD38 and/or ZAP-70 expression can be determined using immunohistochemistry or flow cytometry. Evaluation of ZAP-70 expression using flow cytometry can be challenging and is not recommended outside a clinical trial.

Conventional metaphase cytogenetics is difficult in CLL because of the very low proliferative activity of leukemic cells in vitro. Therefore, interphase cytogenetic analysis with FISH has been the standard method to detect chromosomal abnormalities that have important prognostic significance. However, FISH can only detect abnormalities specific to the probes used. Cytokine or CpG oligonucleotide stimulation has been used to promote efficient metaphase analysis. Recent studies have shown that stimulation with CpG oligonucleotide and interleukin-2 is more effective than that with 12-O-tetradecanoylphorbol-13-acetate (TPA) for detecting chromosomal abnormalities in CLL. A prospective study conducted by the CLL Research Consortium confirmed that abnormal clones in CLL are more readily detected with CpG oligonucleotide stimulation than with traditional B-cell mitogens, and the clonal abnormalities revealed by CpG-stimulated metaphase cytogenetics are consistent with those detected with interphase FISH and are reproducible among different cytogenetic laboratories. However, the use of CpG stimulation for CLL cytogenetics is not yet universally available.

**Workup**

The workup for CLL/SLL is similar to that for other lymphoid neoplasms. Quantitative immunoglobulins may be particularly informative in patients with recurrent infections. Measurement of β₂-microglobulin may provide useful prognostic information. Although classically the pattern of bone marrow involvement (diffuse vs. nodular) had prognostic significance, this is no longer a factor when more reliable prognostic markers are used, such as IGHV mutation (or its surrogate ZAP-70) and cytogenetic abnormalities determined with FISH, all of which can be obtained through analysis of circulating lymphocytes. Thus, bone marrow biopsy is no longer considered a required part of evaluation for patients with CLL, although it remains useful in evaluating the cause of cytopenias.

CT scans are useful for following and monitoring disease progression when peripheral adenopathy is present. For anemic patients, reticulocyte counts and a direct Coombs test should be performed to evaluate for the possibility of hemolysis. PET scan is generally not useful in CLL but can assist in directing nodal biopsy if Richter’s transformation is suspected.

**Response Criteria**

The NCI-sponsored working group first published the guidelines for the diagnosis and treatment of CLL in 1996. Recent developments in the use of prognostic markers and treatment options for CLL have led to revision of these guidelines, particularly the response criteria. Complete and partial responses are considered clinically beneficial. Relapsed disease progresses after 12 months or more of complete or partial response, whereas refractory disease does not respond to purine analog-based therapy or progresses within 12 months after this therapy is given.

**Treatment Options**

**First-Line Therapy**: In earlier clinical trials, chlorambucil plus prednisone had comparable efficacy to CVP (cyclophosphamide, vincristine, and prednisone) and CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimens in patients with advanced CLL. In the CALGB 9011 study, 509 patients were randomized to first-line therapy with either fludarabine, chlorambucil, or the combination. The combination arm was stopped because of excessive toxicity. Complete remission (20% vs. 4% for chlorambucil), partial remission (43% vs. 33% for chlorambucil), median duration of remission (25 vs. 14 months for chlorambucil), and median progression-free survival (20 vs. 14 months for chlorambucil) were significantly better in patients treated with fludarabine. The study found no significant differences in overall survival between the
fludarabine and chlorambucil arms (66 vs. 56 months for chlorambucil).

In a phase III randomized trial conducted by the German CLL Study Group (GCLLSG), fludarabine was significantly better than chlorambucil in terms of overall response rate (72% vs. 51%, respectively) and time to treatment failure (18 vs. 11 months, respectively) in patients older than 65 years (median age, 70 years), but fludarabine showed no survival benefit over chlorambucil (overall and progression-free survivals were 46 and 19 months, respectively, for fludarabine, and 64 and 19 months, respectively, for chlorambucil).100

A European randomized study compared fludarabine with 2 alkylating agent–based combination regimens, CAP (cyclophosphamide, doxorubicin, and prednisone) and CHOP, as first-line treatment in patients with advanced CLL.101 Fludarabine and CHOP produced similar overall remission rates (71%) to CAP (58%), but fludarabine was better tolerated than CHOP. In large randomized trials, the combination of fludarabine and cyclophosphamide (FC) was associated with an increase in overall response, complete response, and progression-free survival compared with fludarabine alone.70,102,103

CALGB study 9712 compared the efficacy of fludarabine with concurrent or sequential administration of rituximab in untreated patients with CLL.104,105 The concurrent regimen was associated with a higher overall response rate (90% vs. 77% for the sequential regimen) at the expense of higher grade 3 or 4 toxicity. However, comparison of the outcomes of patients treated with fludarabine alone in the CALGB 9011 trial and the pooled results from the CALGB 9712 study suggest that the addition of rituximab to fludarabine prolongs progression-free and overall survival.106

The combination of fludarabine, cyclophosphamide, and rituximab (FCR) evaluated at MD Anderson Cancer Center as initial therapy produced high overall and complete response rates.107-109 At a median follow-up of 6 years, the overall response rate was 95% (72% complete response) for the 300 study patients.108 Recently, a large international randomized phase III clinical trial (CLL8) showed that the addition of rituximab to fludarabine-based chemotherapy improved response rates and progression-free and overall survival in patients with CLL compared with fludarabine-based chemotherapy alone.110

In this trial, 817 patients with previously untreated CD20+ CLL were randomized to 6 courses of either FCR or FC regimen. At 3 years after randomization, the progression-free and overall survival rates were 65% and 87%, respectively, for patients randomized to FCR compared with 45% and 82.5%, respectively, for those who received FC. FCR also induced a higher overall response rate (95% vs. 88%) and more complete responses (44% vs. 22%) than FC. Median progression-free survival was 52 and 33 months for FCR and FC, respectively. Based on the results of this trial, the FDA approved rituximab in combination with FC for patients with previously untreated CD20+ CLL.

In a trial initiated by the CLL Research Consortium, pentostatin, cyclophosphamide, and rituximab showed significant clinical activity despite poor risk–based prognoses in previously untreated patients.111 Responses were observed in 91% of patients (41% complete response, 21% nodular partial response, and 28% partial response). In a subsequent study, the combination of higher-dose pentostatin and rituximab resulted in an overall response rate of 76%, with a complete response rate of 27%.112 However, in historical comparison, the response rates were higher and median treatment-free survival (16 vs. 30 months for pentostatin, cyclophosphamide, and rituximab) was notably longer in all accrued patients treated with pentostatin, cyclophosphamide, and rituximab compared with pentostatin and rituximab.

Bendamustine is an alkylating agent with a low cross-resistance with other alkylating agents (chlorambucil, cyclophosphamide, ifosfamide) and fludarabine. A pivotal phase III randomized study (n = 319) comparing bendamustine with chlorambucil in patients with untreated CLL113,114 showed that the overall response (68% vs. 31%, respectively) and complete response rates (31% vs. 2%, respectively) were significantly higher for bendamustine. Median progression-free survival (22 vs. 8.3 months for chlorambucil) and median duration of remission (22 vs. 8 months with chlorambucil) were also better for bendamustine. However, no differences were seen in overall survival between the groups, and the efficacy of bendamustine compared with first-line therapies other than chlorambucil has not yet been established. In a multicenter phase II trial (CLL2M) from the GCLLSG, bendamustine in combination with rituximab (BR) resulted in an overall response
rate of 91% (33% complete response and 55% partial response) for the entire study population (n = 117) with untreated CLL.\textsuperscript{115} The GCLLSG is currently comparing FCR and BR (CLL10).

Alemtuzumab, a monoclonal antibody targeting CD52, has been effective as a first-line treatment for patients with CLL.\textsuperscript{116,117} An international multicenter study (CAM307) that randomized 297 patients with CLL to receive either alemtuzumab or chlorambucil as first-line treatment\textsuperscript{117} showed that alemtuzumab had superior progression-free survival, with a 42% reduction in risk of progression or death. The overall response rate for alemtuzumab was significantly better than for chlorambucil (83% with 24% complete response vs. 55% with 2% complete response). In patients with del(17p), the overall response rate and median progression-free survival for alemtuzumab were 64% and 11 months, respectively, which were higher than those observed with chlorambucil (20% and 2 months, respectively).

Relapsed or Refractory Disease: The FCR regimen also induced higher response rates in previously treated patients (n = 177).\textsuperscript{118} The overall response rate was 73% (complete remission, nodular partial remission, and partial remissions were achieved in 25%, 16%, and 32% of patients, respectively). Recently, the REACH (Rituximab in the Study of Relapsed Chronic Lymphocytic Leukemia) trial compared 6 cycles of FCR with 6 cycles of FC in 552 patients with previously treated CLL.\textsuperscript{119} After a median follow-up of 25 months, patients in the FCR group had significantly improved progression-free survival compared with those in the FC group (31 vs. 21 months, respectively). The overall response rate was also significantly higher for the FCR regimen (70%, including 24% complete response and 46% partial response vs. 58%, including 13% complete response and 45% partial response for FC regimen). At median follow-up of 25 months, overall survival was not significantly improved for FCR. Based on the results of this trial, the FDA approved rituximab in combination with FC for patients with previously treated CD20+ CLL.

The combination of pentostatin and cyclophosphamide (PC) with or without rituximab (R) has shown significant activity in previously treated patients with relapsed or refractory disease.\textsuperscript{120,121} In a small number of previously treated patients (n = 46), the response rates were similar for PC and PCR. However, based on a historical retrospective comparison with PC regimen, PCR has a longer median duration of response (25 vs. 7 months) and median survival (44 vs. 16 months).\textsuperscript{120}

In a phase I/II trial, the combination of oxaliplatin, fludarabine, cytarabine, and rituximab (OFAR) was highly active in fludarabine-refractory patients with CLL and those with Richter’s syndrome.\textsuperscript{122,123} The overall response rates were 50% in patients with Richter’s syndrome and 33% in those with fludarabine-refractory CLL.\textsuperscript{122} Responses were achieved in 7 of 20 patients (35%) with del(17p), 2 of 7 patients (29%) with del(11q), all 4 patients with trisomy 12, and 2 of 5 patients (40%) with del(13q). The median response duration was 10 months. The overall response rate in patients aged 70 years or older (n = 14) was 50%.

The GCLLSG conducted a trial on BR for patients with relapsed CLL, which resulted in an overall response rate of 77% in 62 evaluable patients with relapsed or refractory disease.\textsuperscript{124} Complete and partial responses were seen in 14.5% and 63% of patients, respectively. Stable disease was achieved in 18% of patients, and 5% had progressive disease.

High-dose methylprednisolone (HDMP) with rituximab is well tolerated and an effective therapy for patients with refractory CLL, including those with unfavorable prognostic features.\textsuperscript{125–127} In a study of 28 patients with fludarabine-refractory CLL, the overall response rate was 96% (32% complete response).\textsuperscript{126} In a follow-up of 37 patients with CLL treated with HDMP and rituximab at Mayo Clinic, 29 (78%) had an objective response, including 5 of 9 patients with del(17p),\textsuperscript{125} and 8 (22%) had a complete clinical response. The 3-year survival rate was 41%. One study showed that although the combination of HDMP and rituximab induced superior overall (93%) and complete (14%) response rates compared with HDMP alone (43% and 0%, respectively) in heavily pretreated patients with advanced disease, it was also associated with a high rate of opportunistic infections.\textsuperscript{127}

Alemtuzumab also induced significant responses in patients for whom fludarabine-based therapy failed.\textsuperscript{128} Overall objective response in the intent-to-treat population (n = 93) was 33% (2% complete response and 31% partial response). Median time to progression was 4.7 months overall (9.5 months for responders) and median overall survival was 16
months (32 months for responders). Other studies have also shown that alemtuzumab is effective in patients with fludarabine-refractory CLL and del(17p) or p53 gene mutations. Subcutaneous alemtuzumab seems to be as effective and safe as intravenous alemtuzumab in patients with advanced-stage relapsed or refractory CLL. In a recent retrospective analysis, favorable overall response rate and progression-free and overall survivals (49%, and 7 and 19 months, respectively) were observed with alemtuzumab in pretreated patients with del(17p).

However, nodal sites of disease have generally not responded well with single-agent alemtuzumab. Combinations of alemtuzumab and fludarabine, alemtuzumab and rituximab, and cyclophosphamide, fludarabine, alemtuzumab, and rituximab (CFAR) have shown promising results in patients with relapsed or refractory disease. Ofatumumab, a human CD20 monoclonal antibody, was found to be well tolerated in patients with relapsed or refractory CLL in a phase I/II study. In October 2009, ofatumumab was approved by the FDA for treatment of patients with CLL refractory to fludarabine and alemtuzumab based on the interim analysis of the pivotal international clinical trial, which included data from 138 patients with fludarabine- and alemtuzumab-refractory (FA-ref) CLL or patients with fludarabine-refractory CLL with bulky lymphadenopathy (BF-ref). In the interim analysis, the overall response rate was 58% and 47% in the FA-ref and BF-ref groups, respectively. The final results from the pivotal trial showed the safety and efficacy of ofatumumab in this heavily pretreated patient population. Median progression-free survival was 5.5 months for both groups. The median overall survival was 14 and 17 months for the FA-ref and BF-ref groups, respectively.

Allogeneic HSCT has been shown to improve the prognosis in patients with advanced disease and those with poor-risk features. In a retrospective analysis of the European Group for Blood and Marrow Transplantation (EBMT), allogeneic HSCT induced long-term remission in patients with del(17p). At median follow-up of 39 months, 3-year overall and progression-free survival rates were 44% and 37%, respectively. Final results of the prospective multicenter trial (GCLLSG CLL3X study) also showed that nonmyeloablative allogeneic stem cell transplant can induce sustained minimal residual disease–negative event-free survival in a significant proportion of patients with del(17p). Patients with and without del(17p) had 3-year event-free survivals rates of 43% and 41%, respectively. Of 13 patients with del(17p), 5 were minimal residual disease–negative at 12 months. This study also identified refractory disease at the time of transplant as a negative prognostic factor for overall and event-free survivals. It is understood that studies involving allogeneic HSCTs are subject to strong selection biases. Nonetheless, available evidence from nonrandomized clinical studies suggests that allogeneic HSCT is an effective treatment option for patients refractory to chemoimmunotherapy or who develop recurrence within 12 months after purine analog treatment.

NCCN Recommendations

Localized SLL (Ann Arbor Stage I): Locoregional radiation therapy (RT) is an appropriate induction therapy for this group of patients. In rare patients, RT may be contraindicated or may be suboptimal therapy because of the presence of comorbidities or potential for long-term toxicity. Patients with localized SLL that has progressed after initial RT are treated as described for patients with SLL (Ann Arbor stage II–IV).

SLL (Ann Arbor Stage II–IV) or CLL (Rai Stages 0–IV): In some patients, early-stage disease may have an indolent course, and in others it may progress rapidly to advanced disease requiring immediate treatment. Absolute lymphocyte count alone is not an indication for treatment unless it is greater than 200 to 300 x 10^9/L or symptoms related to leukostasis are present. Therefore, in patients with SLL (Ann Arbor stage II–IV) or CLL (Rai stages 0–II), treatment options depend on the presence or absence of the following indications: significant disease-related symptoms, including severe fatigue, weight loss, night sweats, and fever without infection; threatened end-organ function; progressive bulky disease (enlarged spleen or lymph nodes); lymphocyte doubling time of 6 months or less; or progression to more advanced-stage CLL with progressive anemia or thrombocytopenia. Patients with no indications for treatment can be observed until disease progression or the appearance of any indications for treatment. Patients with advanced-stage CLL (Rai stage III–IV) require immediate treatment.

Given the incurability of the disease, these guidelines recommend enrollment in clinical tri-
als, when locally available, as the preferred first-line therapy for all patients. For patients presenting with indications for treatment and not eligible or do not have access to clinical trials, the treatment recommendations included in the guidelines are based on the presence or absence of del(17p) or del(11q), age, and performance status of the patient. Reevaluation of FISH is necessary to direct treatment options in patients with indications for treatment.

**CLL/SLL Without del(17p) or del(11q): First-Line Therapy:** Patients are stratified according to their age and associated comorbid conditions. Comorbidities can be assessed using the cumulative illness rating scale.153

For frail patients with significant comorbidities and unable to tolerate purine analogs, options include monotherapy with chlorambucil (with or without prednisone), rituximab, or pulse corticosteroids.

For patients aged 70 years or older, or those younger with significant comorbidities, these NCCN Guidelines include alkylating agent–based chemotherapy or chemoimmunotherapy; monotherapy with alemtuzumab or rituximab; fludarabine with or without rituximab; or cladribine as options. Based on the results of the CLL8 trial,110 the guidelines include rituximab in combination with purine analog–based chemotherapy or bendamustine as options for patients aged 70 years or younger or older patients without significant comorbidities. See Suggested Treatment Regimens for CLL Without del(11q) or del(17p) on page 493 for a list of specific regimens.

Based on several trials, chemoimmunotherapy has emerged as the standard of care in patients younger than 70 without significant comorbidities.105,110 A randomized comparison of FCR versus PCR showed a higher complete response rate for FCR, but the overall response and overall survival rates were no different between the regimens.154 Both FCR and FR are highly active regimens, but category 1 evidence is not available to help choose between these 2 regimens. In the absence of del(11q), whether these regimens have different long-term outcomes is uncertain.

**Second-Line Therapy:** In patients for whom first-line therapy fails, treatment options depend on the duration of response after first-line therapy. Among patients in whom initial therapy with FCR chemoinmunotherapy failed, those with a time to treatment failure of 3 years or more had better median survival (44 months) than those with a time to treatment failure of less than 3 years.155 If the response duration is more than 3 years (long response), these NCCN Guidelines recommend additional cycles of the same regimen that was used as first-line therapy for all patients.

If the response duration is less than 2 years (short response), treatment options depend on patient age. For patients 70 years or older, or younger patients with comorbidities, options include reduced-dose FCR or PCR; bendamustine with or without rituximab; HDMP with rituximab; monotherapy with ofatumumab; alemtuzumab with or without rituximab; or dose-dense rituximab. For patients younger than 70 or older patients without significant comorbidities, the guidelines have included chemoimmunotherapy, monotherapy with ofatumumab, or alemtuzumab with or without rituximab as options. See Suggested Treatment Regimens for CLL Without del(11q) or del(17p) on page 493 for a list of specific regimens.

Allogeneic HSCT can be considered for patients with short response but would generally be used after reinduction of remission.

**CLL/SLL With del(17p):** Del(17p) is associated with low response rates with all treatments. Because no standard treatment exists, a clinical trial is recommended. First-line therapy options include FCR or FR, HDMP plus rituximab, alemtuzumab with or without rituximab, or BR.

Patients who have experienced a complete or partial response to first-line therapy should be treated with allogeneic HSCT if they are eligible. Patients experiencing a complete or partial response after transplant can either be observed or enrolled in a clinical trial. Alternatively, patients with a partial response could also be treated with chemoimmunotherapy. See Suggested Treatment Regimens for CLL With del(17p) on page 494 for a list of specific regimens.

Patients who experience no response to first-line therapy, experience response to first-line therapy but are not eligible for allogeneic HSCT, or experience no response to transplant should be enrolled in a clinical trial or can be treated with second-line therapy for relapsed or refractory disease. The guidelines have included chemoimmunotherapy, monotherapy with ofatumumab, alemtuzumab with or without rituximab, HDMP, or bendamustine with or without rituximab as options. See Suggested Treatment Regimens for CLL With del(17p) on page 494 for a list of specific regimens.
Non-Hodgkin’s Lymphomas

**CLL/SLL With del(11q):** First-line therapy options are based on the age and associated comorbid conditions. If patients have a del(11q), an alkylator must be included in the regimen. Response rates and duration improve when an alkylator is added to a purine analog. In patients older than 70 or with significant comorbidities, single-agent alemtuzumab or rituximab should be used only if an alkylator is considered unsafe or was intolerable. For a list of specific regimens, see Suggested Treatment Regimens for CLL With del(11q), page 495.

Patients who experience complete response to first-line therapy can either be observed until disease progression or enrolled in a clinical trial. For those experiencing disease progression after complete response, treatment options depend on the duration of response to first-line therapy. (See Suggested Treatment Regimens for CLL With del(11q), page 495, for a list of specific regimens.) Patients with a partial response to first-line therapy should be treated with allogeneic HSCT, if they are eligible. After transplant, treatment options are similar to those described for patients with del(17p).

Patients with no response to first-line therapy, or those with a partial response to first-line therapy but not eligible for allogenic HSCT should be enrolled in clinical trials or treated with second-line therapy for relapsed or refractory disease. (See Suggested Treatment Regimens for CLL With del(11q), page 495, for a list of specific regimens.)

**Histologic Transformation to DLBCL or Hodgkin Lymphoma:** Approximately 2% to 5% of patients with CLL will develop Richter’s syndrome (transformation into DLBCL or Hodgkin lymphoma) during the course of treatment. The incidence of transformation increases with the number of prior regimens. Patients with Richter’s syndrome should be treated with a combination of chemoimmunotherapy regimens initially developed for DLBCL. In addition to these regimens, the guidelines have also included R-hyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine, followed by rituximab) as an option for patients with histologic transformation and for relapsed or refractory CLL.

Allogeneic HSCT has also shown promising results in patients with Richter’s syndrome who experience response to initial therapy. In a nonrandomized comparison, the estimated cumulative 3-year survival rate was significantly higher (75%) in patients who underwent allogeneic HSCT after experiencing complete or partial response to initial therapy than in those who experienced response to initial therapy and underwent no allogeneic HSCT or who underwent allogeneic HSCT for relapsed or refractory Richter’s syndrome (27% and 21%, respectively). Allogeneic HSCT can be considered after initial therapy.

**Supportive Care for Patients With CLL**

**Infections:** Infectious complications in patients with CLL are influenced by the reduction in immunoglobulin levels and are more common in previously treated patients. Hypoglobulinemia is present in 38% of patients up to 3 years before CLL diagnosis. In a retrospective analysis, 89% of patients with fludarabine-refractory CLL developed infectious complications (78% bacterial and 12% viral). IVIG, antibacterial or antiviral prophylaxis, and vaccinations are the 3 options available for reducing infectious complications.

In randomized studies, IVIG has been associated with a significant decrease in the occurrence of infections but no improvement in overall survival. Antibacterial prophylaxis may be a useful alternative option. Protein and conjugate vaccines have been shown to induce better responses than plain polysaccharide vaccines. Some studies have reported that H$_2$-receptor blockers can enhance vaccine response.

In selected patients (serum IgG < 500 mg/dL) with recurrent sinopulmonary infections requiring intravenous antibiotics or hospitalization, the NCCN Guidelines recommend monitoring IVIG levels and administering 0.3 to 0.5 g/kg of IVIG monthly to maintain nadir levels of approximately 500 mg/dL. Antibacterial prophylaxis is also appropriate for managing infections. Antiviral and pneumocystis prophylaxis is recommended for patients receiving purine-analog and/or alemtuzumab during treatment and thereafter. Acyclovir or its equivalent is recommended for herpes virus, and sulfamethoxazole trimethoprim or equivalent is recommended for pneumocystis carinii pneumonia. Annual influenza vaccine and pneumococcal vaccine (every 5 years) is recommended for all patients. All live vaccines should be avoided. Patients with CLL have a poor immune response to influenza vaccine and therefore should be cautious during influenza season even after vaccination. Patients who have undergone rituximab therapy do not respond to influenza vaccination until B-cell recovery.
Cytomegalovirus Reactivation: Cytomegalovirus reactivation is a well-documented side effect in patients receiving alemtuzumab.\textsuperscript{116,128,174} Cytomegalovirus reactivation is associated with relatively mild or no symptoms when prophylactic measures are used during treatment with alemtuzumab. The current appropriate management is controversial; some clinicians use ganciclovir (oral or intravenous) prophylactically if viremia is present, others use it only if the viral load is increasing.\textsuperscript{175,176}

Clinicians must be aware of the high risk of cytomegalovirus reactivation. Regularly monitoring patients for cytomegalovirus reactivation using PCR is an effective approach.\textsuperscript{177} These NCCN Guidelines recommend cytomegalovirus viremia monitoring (every 2–3 weeks). Consultation with an infectious disease expert may be necessary.

Autoimmune Cytopenias: Autoimmune hemolytic anemia (AIHA); immune-mediated thrombocytopenia, also known as immune thrombocytopenic purpura (ITP); and pure red blood cell aplasia (PRCA) are the most frequent autoimmune cytopenias in patients with CLL.\textsuperscript{178,179}

AIHA is the most common form of autoimmune cytopenia. The direct antiglobulin test (DAT) has been used to diagnose AIHA. However, most patients with AIHA have negative DAT, and therefore additional markers, such as low haptoglobin and elevated reticulocyte and LDH, are required to confirm the diagnosis.\textsuperscript{180} Patients with advanced disease, unmutated IGHV, increased serum β₂-microglobulin level, and high expression of ZAP-70 are also at a higher risk of developing AIHA.\textsuperscript{181–183} ITP in patients with CLL is associated with poorer survival independent of common clinical prognostic variables. In a recent Italian study, high WBC count, unmutated IGHV, and DAT and ZAP-70 positivity were associated with the development of ITP in patients with CLL.\textsuperscript{184} PRCA is less common in these patients.

Bone marrow evaluation is recommended to confirm the diagnosis of autoimmune cytopenia. Evaluation of parvovirus B19 is also recommended to exclude parvovirus-induced PRCA. AIHA and ITP can be managed with corticosteroids in most cases. IVIG, cyclosporin,\textsuperscript{185} and splenectomy should be used in steroid-refractory cases. Rituximab has also been effective for the treatment of autoimmune cytopenias.\textsuperscript{186–192} Corticosteroids tend to be less effective in PRCA than in ITP or AIHA. If corticosteroids are not effective, cyclosporin can be used. In very refractory cases, allogeneic HSCT maybe necessary. More recently, synthetic thrombopoietin-like agents, such as romiplostim and eltrombopag, have shown promising results in the treatment of thrombocytopenia associated with ITP.\textsuperscript{193–195} In 2008, both romiplostim and eltrombopag received FDA approval for the treatment of thrombocytopenia in patients with ITP refractory to steroids, IVIG, and splenectomy.

Purine analog–based therapy has been associated with AIHA. Recent studies have reported a higher incidence of AIHA in patients treated with fludarabine or chlorambucil than in those treated with fludarabine-based combination regimens (FC or FCR).\textsuperscript{186,196} AIHA should not preclude the use of combination therapy containing fludarabine, and patients should be observed carefully. In the case of severe AIHA, fludarabine therapy should be discontinued and subsequent use avoided.

Tumor Lysis Syndrome: Patients with CLL and high WBC count may occasionally experience TLS and should be managed as outlined in Tumor Lysis Syndrome, page 524.

Follicular Lymphoma

Diagnosis

FL is the most common indolent subtype of NHL, accounting for approximately 22% of all newly diagnosed cases. Approximately 90% of the cases have a t(14;18) translocation, which juxtaposes BCL2 with the IGHV locus and results in the deregulated expression of BCL2.

FL has a characteristic immunophenotype that includes CD20+, CD10+, BCL2+, CD23+/-, CD43+, CD5−, CCND1−, and BCL6+. Rare cases of FL may be CD10− or BCL2−. In young patients with localized BCL2− disease, pediatric FL may be considered. This diagnosis is easily established based on histology, but immunophenotyping is encouraged to rule out a nodular MCL or SLL. Low-grade FL with a high proliferation index determined through Ki-67 immunostaining has been shown to be associated with aggressive clinical behavior, but no evidence shows that it should guide selection of therapy.\textsuperscript{197,198} Molecular genetic analysis to detect BCL2 rearrangement; cytogenetics or FISH to identify t(14;18); and paraffin section immunohistochemistry for Ki-67 will be useful under certain circumstances.
In FL, pathologic grading according to the number of centroblasts is considered to be a clinical predictor of outcome. In the 2001 WHO classification, 3 grades were recommended: FL1, FL2, and FL3; FL3 could be optionally stratified into 3A (centrocytes still present) or 3B (sheets of centroblasts). However, clinical outcomes for patients with FL1 and FL2 do not differ and classification is unreliable. Therefore, the updated 2008 WHO classifies these as one grade (FL1–2).\(^1\)\(^6\)\(^7\) Hans et al.\(^1\) reported no difference in survival between grade 3A and 3B, whereas patients with FL3 with more than 50% diffuse components had an inferior survival similar to that of those with DLBCL. FL3B with cytogenetic abnormalities of BCL6 (at 3q27) is believed to be genetically more akin to germinal center–type DLBCL than FL1–3A and has a more aggressive clinical course. Patients with FL3B with BCL2 translocation seem to have similar clinical behavior to patients with FL1–3A.\(^2\)\(^0\) Because FL3B is rare, in most studies clinical behavior of FL3 is based mainly on FL3A cases. The 2008 WHO classification mandates stratifying FL3 into either 3A or 3B. FL is thus still divided into 3 grades (FL1–2, FL3A, and FL3B) based on the number of centroblasts. Any diffuse areas in FL should be given a separate diagnosis of DLBCL if they meet the criteria for FL3A or 3B.

The Follicular Lymphoma International Prognostic Index (FLIPI) is based on patient age, Ann Arbor stage, number of involved nodal sites involved, hemoglobin levels, and serum LDH levels.\(^2\)\(^1\) In the National LymphoCare study, which analyzed the treatment options and outcomes of 2728 patients with newly diagnosed FL, FLIPI was used to classify patients into 3 distinct groups, with survival ranging from 52% to 90% at 5 years.\(^2\)\(^2\) In a recent study conducted by the International Follicular Lymphoma Prognostic Factor Project, a prognostic model was developed from prospective accumulated data that includes age, hemoglobin, dimension of the longest lymph node, \(\beta_2\)-microglobulin, and bone marrow involvement. FLIPI2 was highly predictive of treatment outcome in patients with newly diagnosed FL treated with chemoimmunotherapy.\(^2\)\(^3\) With follow-up to date, FLIPI2 does not predict for overall survival; furthermore, it is only applicable to patients requiring therapy. Both the FLIPI1 and -2 predict for prognosis, but they have not yet been established as a means of selecting treatment options.

### Workup

The diagnostic workup for FL is similar to that for other indolent lymphomas. Most patients present with disseminated disease. The approach to therapy differs dramatically for localized and disseminated disease. Bone marrow biopsy with aspirate is essential to document clinical stage I and II disease. This can be deferred if observation is the initial treatment option. Most NCCN investigators routinely use chest, abdominal, and pelvic CT as part of the diagnostic evaluation. Neck CT may also help define the extent of local disease. In patients presenting with what appears to be localized disease, a PET scan may help identify occult sites of disease or be useful if concern exists about histologic transformation.\(^2\)\(^4\) PET does not replace histologic confirmation of the diagnosis; however, areas with discordant high FDG-avidity represent the most likely sites of transformation.

### Treatment Options Based on Clinical Stage

The guidelines for FL apply to FL1 and FL2. FL3A and FL3B are commonly treated according to guidelines for DLBCL. In most centers, the proportion of patients diagnosed with FL3 is greater than that previously diagnosed as follicular large cell lymphoma in the IWF.

#### Stages I and II:

Involved-field RT (IFRT; 24–30 Gy, with an additional 6 Gy in selected patients with bulky disease) is the preferred treatment for patients with stage I or contiguous stage II disease. In a retrospective analysis of 43 patients with stage I and II disease, carefully selected patients (meeting criteria of large abdominal radiation field, advanced age, concern for xerostomia or patient refusal) who did not undergo immediate treatment had comparable outcomes to those treated with RT.\(^2\)\(^5\) In selected cases in which toxicity of IFRT outweighs the potential clinical benefit, observation may be appropriate. Alternate treatment options include immunotherapy with or without chemotherapy with or without RT. The addition of cyclophosphamide, vincristine, prednisone, and bleomycin (COP-bleomycin) or CHOP-bleomycin improved failure-free survival but did not impact overall survival in patients with early-stage disease.\(^2\)\(^6\) The addition of adjuvant CHOP to RT did not improve relapse-free survival in patients with early-stage, low-grade lymphoma.\(^2\)\(^7\) Therefore, chemotherapy plus RT is included as a category 2B recommendation.
For patients with a partial or complete response, clinical follow-up with examination and laboratory assessment is initially performed every 3 months, with repeat imaging every 6 months or as clinically indicated. Patients with no response to initial therapy should be managed in the same manner as those with advanced disease.

**Stage II (Bulky Disease) and Stages III and IV:** Rituximab has shown single-agent activity in previously untreated patients and in those with relapsed or refractory disease.\(^{208–210}\) The addition of rituximab to combination chemotherapy regimens has consistently increased the overall response rate, response duration, and progression-free survival. In addition, some studies have shown a benefit in overall survival, with a recent meta-analysis confirming this despite what is still limited follow-up for FL.\(^{211}\)

A small study evaluating the safety and efficacy of R-CHOP showed excellent long-term results.\(^{212,213}\) A prospective randomized phase III study in 428 patients by the German Low-Grade Lymphoma Study Group (GLSG) established the superiority of R-CHOP over CHOP in treatment-naive patients. R-CHOP was associated with a 60% reduction in the relative risk for treatment failure, significantly prolonged time to treatment failure, higher overall response rate, and prolonged duration of remission.\(^{214}\) Overall survival analysis is complicated by a second randomization that included high-dose therapy followed by autologous stem cell rescue (HDT/ASCR). In this study, overall survival was the same with and without rituximab, if there was consolidation with HDT/ASCR. However, overall survival was significantly improved for patients treated with R-CHOP followed by interferon compared with those treated with CHOP followed by interferon. R-CHOP also improved outcome of elderly patients with previously untreated FL.\(^{215}\)

The addition of rituximab to CVP (cyclophosphamide, vincristine, and prednisone) chemotherapy (R-CVP) significantly improved outcome in patients with previously untreated FL, with no significant increase in toxicity.\(^{216}\) At a median follow-up of 53 months, R-CVP was associated with an improved overall response rate (81% vs. 57%), median time to progression (34 vs. 15 months), and 4-year overall survival (83% vs. 77%).\(^{217}\)

The addition of rituximab to fludarabine or fludarabine-based combination has improved outcomes in various clinical studies.\(^{218–221}\) In a prospective randomized trial, the FCMR regimen (fludarabine, cyclophosphamide, mitoxantrone, and rituximab) was associated with superior outcomes in patients with relapsed or refractory FL and MCL.\(^{219}\) In another randomized trial, concurrent administration of rituximab with the FND regimen (fludarabine, mitoxantrone, and dexamethasone) resulted in a significantly higher 3-year failure-free survival rate (84% vs. 59% for sequential arm) in a subset of patients with FL.\(^{220}\)

Bendamustine, as a single agent or in combination with rituximab (BR), has shown promising results with acceptable toxicity in both newly diagnosed and heavily pretreated patients with relapsed or refractory indolent or mantle cell histologies and transformed NHL.\(^{222–226}\) A randomized phase III study conducted by the Study Group Indolent Lymphomas (StiL) compared BR with R-CHOP in patients with advanced follicular, indolent, and mantle cell lymphomas. The overall response rate was similar in both arms, although the complete response rate was significantly higher in the BR arm (40% vs. 31%).\(^{222}\) However, patients treated with BR had significantly longer median progression-free (55 vs. 35 months) and event-free survivals (54 vs. 31 months). BR also showed a better toxicity profile. Overall survival is similar.

Radioimmunotherapy with \(^{131}\)I-tositumomab\(^{227–230}\) and \(^{90}\)Y-ibritumomab tiuxetan\(^{231–233}\) was also evaluated in patients with newly diagnosed and those with relapsed, refractory, or histologically transformed FL. Initial treatment with a single 1-week course of \(^{131}\)I-tositumomab induced prolonged clinical and molecular remissions in patients with advanced FL.\(^{227}\) After a median follow-up of 10 years, the median duration of response was 6 years. For the 57 complete responders, median progression-free survival was 11 years;\(^{234}\) 10-year progression-free and overall survival rates were approximately 40% and 82%, respectively. In an international phase II trial, \(^{90}\)Y-ibritumomab used as first-line therapy resulted in an overall response rate of 72% (52% showing a complete response, and 20% showing a partial response) at 12 months after therapy. At a median follow-up of 23 months, the progression-free survival was 18 months.\(^{235}\)

A single course of \(^{131}\)I-tositumomab was significantly more efficacious than the last qualifying chemotherapy in extensively pretreated patients with refractory, low-grade, or transformed NHL.\(^{229}\) The final results of the study showed that \(^{131}\)I-
tositumomab resulted in long-term, durable complete response in a subset of patients who had received no prior rituximab. In a randomized phase III study, 90Y-ibritumomab tiuxetan also produced statistically and clinically significant higher overall response and complete response rates than rituximab alone in patients with relapsed or refractory low-grade, follicular, or transformed lymphoma. At a median follow-up of 44 months, median time to progression (15 vs. 10.2 months) and duration of response (16.7 vs. 11.2 months) were longer in patients treated with 90Y-ibritumomab than those treated with rituximab.

**NCCN Recommendations for Stage II (Bulky Disease) and Stage III and IV:** Despite therapeutic advances that have improved the survival of patients with FL, it remains an incurable disease with conventional therapy. Four prospective randomized trials have failed to show a survival advantage for immediate treatment. Modified Groupe d’Etude des Lymphomes Folliculaires (GELF) criteria are used to decide when to initiate therapy in patients with advanced-stage disease, including symptoms attributable to FL (not limited to B symptoms); threatened end-organ function; cytopenia secondary to lymphoma; bulky disease (a single mass > 7 cm, or 3 or more masses > 3 cm); splenomegaly; and steady progression over at least 6 months. Patient preference should be considered; however, patients wanting treatment without a clinical indication should be referred for an appropriate clinical trial. Treatment selection should be highly individualized according to age, extent of disease, comorbid conditions, and goals of therapy. When choosing an initial therapy, care should be given to avoid excessively myelotoxic regimens in patients who may be candidates for HDT/ASCR. In patients with hepatitis B, treatment with an antiviral should be given if rituximab is used (see Hepatitis B Virus Reactivation, page 523).

**First-Line Therapy:** In the absence of an appropriate clinical trial, patients with indications for treatment should undergo systemic therapy. In selected cases, such as elderly frail patients unable to tolerate chemotherapy, IFRT (4 Gy) may be used for local palliation. Asymptomatic patients, especially those older than 70 years, can be observed. At 36 months after randomization, the results of an interim analysis of the Intergroup trial of rituximab versus a watch-and-wait strategy showed that the estimated progression-free survival was significantly better for asymptomatic patients with stage II and IV non-bulky disease receiving rituximab alone or rituximab followed by rituximab maintenance than those undergoing observation, but no difference was seen in overall survival between the treatment arms. Further follow-up is needed to determine if immediate treatment has an impact on time to second therapy. The panel thought that these data were not sufficiently compelling to indicate a change of practice. The ECOG RESORT trial is examining rituximab maintenance versus rituximab delayed until progression in a similar patient population, and will provide some additional insight.

Based on the reported data, BR, CHOP, or CVP chemotherapy for first-line therapy in patients with advanced FL are all category 1 recommendations. BR has been shown to have less toxicity and a superior progression-free survival compared with R-CHOP; however, overall survival is not different. Furthermore, limited data are available on the risk of secondary myelodysplastic syndromes/acute myeloid leukemia (MDS/AML) after bendamustine. Data from a limited subset of patients suggest that peripheral blood stem cells can be collected after both BR and R-CHOP; more data are needed to confirm this finding. No randomized trials have compared R-CHOP and R-CVP. Therefore, choice of first-line therapy in advanced-stage FL remains a challenge for the clinician. Other suggested regimens include rituximab either as a single agent or in combination with fludarabine-based chemotherapy. Radioimmunotherapy is included as category 2B option for first-line treatment. IFRT (4–30 Gy) with or without systemic therapy can be considered for palliation in patients with locally bulky or symptomatic disease if they are unable to tolerate systemic therapy.

Single-agent rituximab is the preferred first-line therapy for elderly or infirm patients. Single-agent cyclophosphamide had equivalent overall survival and complete response rates as cyclophosphamide-based combination chemotherapy. The NCCN Guidelines also include radioimmunotherapy and alkylating agent–based chemotherapy (cyclophosphamide or chlorambucil) with or without rituximab as alternative options for elderly or infirm patients.

**First-Line Consolidation or Extended Dosing:** Chemotherapy Followed by Radioimmunotherapy: First-line chemotherapy followed by radioimmunotherapy with either 131I-tositumomab or 90Y-ibritumom-
ab 246–249 has been evaluated in several phase II studies. In the SWOG S9911 trial, CHOP followed by 131I-tositumomab resulted in an overall response rate of 91%, including a 69% complete remission rate in patients with previously untreated FL. 244 After a median follow-up of 5 years, the estimated 5-year overall survival and progression-free survival rates were 87% and 67%, respectively. 241 In historical comparison, these statistics were better than those reported for CHOP alone. In a multicenter phase II study in untreated patients with FL, CVP chemotherapy followed by 131I-tositumomab resulted in overall and complete response rates of 100% and 93%, respectively. The 5-year progression-free and overall survival rates were 56% and 83%, respectively. 245

In the international phase III FIT trial (First-Line Indolent Trial), 414 patients with advanced-stage FL responding to first-line induction therapy were randomized to receive either 90Y-ibritumomab or no further treatment. 246 After a median follow-up of 5.5 years, the 5-year progression-free survival rates were 47% and 29%, respectively. Median progression-free survival was 49 and 14 months, respectively. 250 No significant difference was seen in overall survival. The rate of secondary malignancies (MDS/AML) were higher among patients in the consolidation group (3%) than those in the control group (1%). This trial included only a limited number of patients (14%) who received rituximab in combination with chemotherapy as induction therapy. Among these patients, the 5-year progression-free survival rates were 64% and 48%, respectively, for the 90Y-ibritumomab and control groups.

Maintenance Therapy With Rituximab: Prolonged administration of rituximab significantly improved event-free survival in chemotherapy-naive patients experiencing response to rituximab induction, but did not extend overall survival. 251–253 In another study, maintenance rituximab improved progression-free survival (31 vs. 7 months). However, retreatment with rituximab at progression provided the same duration of benefit as maintenance rituximab (31 vs. 27 months). 254 The randomized phase III study (ECOG 1496) showed a progression-free survival benefit for rituximab maintenance in patients with advanced indolent lymphoma responding to first-line chemotherapy. 255 The 3-year progression-free survival rate was 68% for maintenance rituximab compared with 33% for observation for all patients with advanced indolent lymphoma experiencing response or stable disease after CVP chemotherapy. The corresponding progression-free survival rates were 64% and 33%, respectively, for patients with FL. 255

The PRIMA trial prospectively evaluated the role of rituximab maintenance in patients experiencing response to first-line chemotherapy in combination with rituximab (R-CVP, R-CHOP, or FCMR). This study randomized 1018 eligible patients to either observation or rituximab maintenance for 2 years. 256 The interim analysis with a median follow-up of 24 months showed that rituximab maintenance significantly improved progression-free survival (primary end point) compared with observation. After a median follow-up of 36 months, the 3-year progression-free survival rate was 75% in the rituximab maintenance arm and 58% in the observation arm. 257 At 2 years after randomization, 72% of patients in the rituximab maintenance group were experiencing a complete response or complete response unconfirmed 257; however, no significant differences were seen in overall survival. Follow-up is ongoing to evaluate the effect of rituximab maintenance on overall survival.

**NCCN Recommendations:** Patients experiencing complete or partial response to first-line therapy can be observed or treated with consolidation therapy. Based on the results of the PRIMA study, 256 maintenance rituximab up to 2 years is recommended (category 1) for patients experiencing response to first-line chemotherapy in patients receiving induction chemotherapy rather than chemoimmunotherapy. Based on the results of the FIT trial, radioimmunotherapy is recommended (category 1) only for patients who received first-line chemotherapy. 248 The recommendation to limit radioimmunotherapy to patients receiving induction chemotherapy rather than chemoimmunotherapy is based on the small proportion of patients who received chemoimmunotherapy induction in the FIT trial.

**Second-Line Therapy for Relapsed or Progressive Disease:** Frequently, patients experiencing progression after first-line therapy will benefit from a second period of observation. Thus, treatment for relapsed or progressive disease is based on the modified GELF criteria as used in first-line therapy. Progressive disease should be histologically documented to exclude transformations, especially in the presence of rising LDH levels, disproportional growth in one area, development of extranodal disease, or new B symptoms. Nonuniform uptake on a FDG-
PET scan can be an indication of transformation; areas of high standardized uptake value, especially exceeding 13.1, are suspicious for transformation. However, a PET scan does not replace a biopsy; it should be used to direct a biopsy to enhance the diagnostic yield. Options include chemoimmunotherapy regimens used for first-line treatment, the FCMR regimen (category 1), radioimmunotherapy (category 1), or any of the second-line regimens used for patients with DLBCL.

**Second-Line Consolidation or Extended Dosing:**

Two large randomized trials have established that rituximab maintenance after second-line therapy for relapsed/refractory disease provides a progression-free survival advantage over observation for patients treated with chemoimmunotherapy.258–260

In a prospective randomized study by the GLSG, rituximab maintenance after second-line treatment with FCMR significantly prolonged duration of response in patients with recurring or refractory FL and, to a lesser degree, those with MCL.258 In a phase III Intergroup trial (EORTC 20981), maintenance rituximab significantly improved median progression-free and overall survivals in patients with relapsed or resistant FL responding to CHOP or R-CHOP.259 With a median follow-up of 6 years, the 5-year overall survival rate was 74% and 64% in the rituximab maintenance and observation arms, respectively.260

HDT/ASCR has been shown to prolong overall and progression-free survival in patients with relapsed or refractory disease.261–263 The GELA recently conducted a retrospective analysis of patients with relapsed or refractory FL after first-line treatment with chemotherapy alone and found that event-free survival and survival after relapse were superior in those treated with rituximab-containing regimens compared with chemotherapy only–based HDT/ASCR.264 The combination of rituximab-based second-line therapy followed by HDT/ASCR had the best results, with a 90% survival rate after relapse at 5 years. Allogeneic HSCT is associated with high treatment-related mortality rates (30%–38% for myeloablative and 25% for nonmyeloablative).265,266 In a recent report from the Center for International Blood and Marrow Transplant Research, both myeloablative and nonmyeloablative transplant had similar TRM rates, but nonmyeloablative allogeneic HSCT was associated with an increased risk of disease progression.267

**NCCN Recommendations:** Rituximab maintenance is recommended (category 1) for patients in second-line remission. However, the panel recognized that the efficacy of maintenance rituximab in second-line remission would likely be impacted by first-line maintenance. If a patient experienced progression during or within 6 months of first-line maintenance rituximab, the value of maintenance in the second-line is likely minimal. HDT/ASCR is an appropriate consolidative therapy for patients experiencing second or third remission. Allogeneic HSCT may be considered for highly selected patients. For patients receiving consolidation therapy, clinical follow-up is initially recommended every 3 months with repeat imaging every 6 months and/or as clinically indicated.

**Histologic Transformation to DLBCL:** Transformation to DLBCL in patients with FL occurs at a rate of approximately 2% to 3% per year for at least 15 years, with the risk of transformation decreasing thereafter for reasons that remain unclear.268 Transformation to DLBCL is generally associated with a poor clinical outcome. However, patients with limited disease and no previous exposure to chemotherapy can have favorable outcomes similar to those with de novo DLBCL.269 In patients who have had multiple prior therapies, the prognosis is much poorer and enrollment in a clinical trial is the preferred option. In the absence of a clinical trial, treatment options include radioimmunotherapy, chemotherapy with or without rituximab, IFRT, or best supportive care. HDT/ASCR or allogeneic HSCT can be considered for patients with responsive disease after initial treatment.

For patients who have had minimal (IFRT alone or one course of single-agent therapy, including rituximab) or no prior chemotherapy, anthracycline-based chemotherapy with rituximab, IFRT, or best supportive care. HDT/ASCR or allogeneic HSCT can be considered for patients with responsive disease after initial treatment. Alternatively, patients experiencing a complete response to initial therapy can be observed, whereas radioimmunotherapy may be considered for those experiencing a partial response. Patients experiencing no response or progressive disease after initial therapy should be treated with radioimmunotherapy or best supportive care.
DLBCL

Diagnosis

DLBCLs are the most common lymphoid neoplasms in adults. DLBCL, NOS; FL (grade 3); DLBCL coexistent with FL of any grade; DLBCL coexistent with gastric MALT or nongastric MALT lymphoma; intravascular large B-cell lymphoma; DLBCL associated with chronic inflammation; ALK-positive DLBCL; EBV-positive DLBCL of the elderly; and T-cell/histiocyte–rich large B-cell lymphoma are also managed according to the DLBCL guidelines.

Recent studies with gene expression microarray analysis of DLBCL have revealed significant heterogeneity within this diagnosis.270 Gene expression profiling has been used to identify 3 different subtypes of DLBCL: germinal center B-cell, activated B-cell, and type 3, which includes primary mediastinal B-cell lymphoma (PMBL) and cases that cannot be classified as germinal center B-cell or activated B-cell subtypes.270 Gene expression profiling is not yet recommended for routine clinical use. However, incorporation of this information into treatment algorithms awaits further investigation. Immunohistochemical markers CD10, BCL6, and IRF4/MUM1 have been reported to recapitulate gene expression profiling, separating patients into tumors derived from germinal center origin (CD10+, or BCL6+, IRF4/MUM1+) and non–germinal center origin (CD10–, IRF4/MUM1+ or BCL6–, IRF4/MUM1–).271 However, the validity of this classification scheme has been questioned. An improved immunohistochemical algorithm has been proposed that includes GCET1, FOXP1, BCL6, IRF4/MUM1, and CD10.272 Further work is necessary to validate the robustness of this new algorithm to distinguish between germinal center vs. non–germinal center subtypes.

The typical immunophenotype is CD20+, CD45+, and CD3–. The recommended immunophenotyping panel includes CD20, CD3, CD5, CD10, CD45, BCL2, BCL6, and IRF4/MUM1. When available, GCET1 and FOXP1 can provide information necessary for the Choi immunohistochemical cell of origin algorithm. Additional markers such as CD138, cyclin D1, ALK1, EBV, and HTLV may be useful under certain circumstances to establish the subtype.

Workup

The staging workup is designed to identify all sites of known disease and determine prognosis based on known clinical risk factors. Risk factors used by the International Prognostic Index (IPI) include age, disease stage, serum LDH level, performance status, and number of extranodal disease sites. In patients aged 60 years or younger, these factors include tumor stage, performance status, and serum LDH level. The IPI and age-adjusted IPI can be used to identify specific groups of patients who are more or less likely to be cured with standard therapy. PET or PET-CT scans have a more clear-cut role in selected cases of DLBCL than in other lymphoid neoplasms. PET scans are particularly informative during initial staging, in which upstaging results in altered therapy approximately 9% of the time, and in response evaluation after treatment because they can distinguish residual fibrotic masses from masses containing viable tumor. PET scans have now been incorporated into the response criteria, and availability of a baseline study is necessary for optimal interpretation of the posttreatment study. In some centers, β2-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, epidural, or bone marrow (with large cells), or with HIV-associated lymphoma, or who have 2 or more extranodal sites. Diagnostic yield is improved by flow cytometric analysis of cerebrospinal fluid.

Treatment Options by Clinical Stage

Treatment options for DLBCL differ between patients with localized (Ann Arbor stage I–II) and advanced (Ann Arbor stage III–IV) disease. Prognosis is extremely good for patients with no adverse risk factors (elevated LDH, stage II bulky disease, > 60 years, or ECOG performance status ≥ 2). Patients with advanced disease should be enrolled in clinical trials whenever possible.

Stages I and II: In the SWOG 8736 study, 3 cycles of CHOP followed by IFRT produced significantly better progression-free (5-year estimated progression-free survival: 77% vs. 64% for CHOP alone) and overall survival rates (82% vs. 72% for CHOP alone) than 8 cycles of CHOP alone in patients with localized aggressive NHL; however, this difference disappeared with further follow-up. The benefit of CHOP (3 cycles) followed by IFRT (5-year overall survival rate of 95%) in patients with limited-stage DLBCL (aged ≤ 60 years with no adverse risk factors) was also confirmed in a series from British Co-
Non-Hodgkin’s Lymphomas

Stages III and IV: R-CHOP-21 chemotherapy has been the standard treatment for patients with advanced-stage DLBCL based on the results of the GELA study (LNH 98-5), which showed that the addition of rituximab to CHOP-21 improved progression-free and overall survivals in elderly patients with advanced DLBCL. In this study, 399 elderly patients (age 60–80 years) were randomized to receive 8 cycles of R-CHOP or CHOP. Long-term follow-up of this study showed that progression-free (36.5% vs. 20%), disease-free (64% vs. 43%), and overall survival rates (43.5% vs. 28%) were statistically significant in favor of R-CHOP at a median follow-up of 10 years. These findings have been confirmed in 3 additional randomized trials, including the MabThera International Trial (MInT; 6 cycles of R-CHOP or CHOP), which extended the findings to young patients with 0 or 1 risk factors according to the IPI; the Dutch HOVON and Nordic Lymphoma group study (8 cycles of R-CHOP-14 or CHOP-14); and the ECOG/CALGB study, which confirmed the findings in patients older than 60 years. The ECOG/CALGB study also showed that maintenance rituximab significantly prolonged failure-free survival in older patients whose disease responded to CHOP chemotherapy, but it did not show any clinical benefit for those whose disease responded to R-CHOP as induction therapy.

Six cycles of dose-dense CHOP (CHOP-14) as first-line therapy was found to be superior to 6 cycles of CHOP-21. In the RICOVER 60 trial, the addition of rituximab to CHOP-14 improved clinical outcomes in elderly patients compared with CHOP-14 alone. In this study, overall survival significantly favored 6 cycles of R-CHOP-14 over 8 cycles (78% and 72.5%, respectively) because of late, non–cancer-related deaths. In patients with a partial response after 4 cycles of chemotherapy, 8 cycles were not better than 6. Ongoing randomized studies are evaluating the role of R-CHOP-14 versus R-CHOP-21.

Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) plus rituximab has shown significant activity in untreated patients with DLBCL. An ongoing phase III randomized study is evaluating dose-adjusted R-EPOCH versus R-CHOP in untreated patients with DLBCL. NCCN Recommendations: Patients with advanced disease are treated with 6 cycles of R-CHOP (cat-

lumbia Cancer Agency. Another randomized trial (ECOG 1484) showed that the addition of RT to CHOP (8 cycles) prolonged disease-free survival in patients with limited stage DLBCL who had experienced a complete response to CHOP alone (6-year disease-free survival was 73% for IFRT and 56% for observation). In the GELA study (LNH 93-4), the addition of RT to 4 cycles of CHOP did not provide any advantage over 4 cycles of CHOP alone for the treatment of elderly patients with low-risk localized aggressive lymphoma. The estimated 5-year event-free survival rates were not different between the groups (61% and 64%, respectively) and the 5-year estimated overall survival rates were 68% and 72%, respectively. However, administration of RT was markedly delayed and 12% of patients in the RT arm did not receive RT.

The efficacy of the addition of rituximab to CHOP (3 cycles) and IFRT has also been reported in patients with limited-stage DLBCL. In the SWOG 0014 study, with the median follow-up of 5 years, the 2- and 4-year progression-free survival rates were 93% and 88%, respectively, for patients with at least one stage modified. The corresponding overall survival rates were 95% and 92%, respectively. In historical comparison, these results were better than the survival rates for patients treated without rituximab (4-year progression-free and overall survival rates were 78% and 88%, respectively). In the GELA study (LNH 93-1), intensified chemotherapy (ACVBP [doxorubicin, cyclophosphamide, vincristine, bleomycin, and prednisone] followed by consolidation with methotrexate, etoposide, ifosfamide, and cytarabine) with or without rituximab was found to be superior to CHOP with or without rituximab (3 cycles) plus RT in patients with low-risk early-stage disease. However, this regimen is also associated with significant toxicity and includes vindesine, which is not available in the United States.

NCCN Recommendations: R-CHOP (3 cycles) with IFRT or R-CHOP (6 cycles) with or without IFRT is recommended for patients with nonbulky disease (< 10 cm). IFRT is recommended for patients who are not candidates for chemotherapy. The addition of RT to a full course of 6 cycles of R-CHOP for patients with no adverse factors is included as a category 2B recommendation. Patients with bulky disease (≥ 10 cm) may be more effectively treated with 6 cycles of R-CHOP with or without locoregional RT (category 1).
egory 1). In selected cases, RT to bulky sites may be beneficial (category 2B). Involvement of paranasal sinus, testis, bone marrow, or 2 or more extranodal sites is associated with a higher risk of central nervous system relapse. Central nervous system prophylaxis with 4 to 8 doses of intrathecal methotrexate and/or cytarabine should be given during the course of treatment, although prophylactic therapy has been suggested to be of value.

R-CHOP with rituximab is preferable because of reduced toxicities; however, other comparable anthracycline-based regimens are acceptable. Suggested alternate options include dose-dense R-CHOP-14 or dose-adjusted EPOCH plus rituximab, both of which are listed as category 2B recommendations. The NCCN Guidelines have included the following regimens as first-line therapy for patients with poor left ventricular function (category 2B):

- CEPP (cyclophosphamide, etoposide, prednisone, and procarbazine) plus rituximab
- CDOP (cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone) plus rituximab
- CNOP (cyclophosphamide, mitoxantrone, vincristine, and prednisone) plus rituximab
- Dose-adjusted EPOCH plus rituximab
- CEOP (cyclophosphamide, etoposide, vincristine, and prednisone) plus rituximab

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 TLS.

**Response Assessment and Follow-Up Therapy**

Interim restaging is performed to identify patients whose disease has not responded or has progressed despite induction therapy. PET scans may be particularly useful in determining whether residual masses represent fibrosis or a viable tumor. A negative PET scan after 2 to 4 cycles of chemotherapy has been associated with an excellent outcome. Patients with negative PET scans have significantly higher 5-year event-free survival rates than those with positive scans (80% vs. 36%, respectively) after induction therapy with CHOP with or without rituximab. However, interim PET scan can produce false-positive results, and some patients treated with chemoimmunotherapy have a favorable long-term outcome despite a positive interim PET scan. A prospective study from Memorial Sloan-Kettering Cancer Center (MSKCC) evaluated the significance of interim PET scans by obtaining biopsies from patients with an interim positive PET. The biopsy showed persistent disease in only 5 of 37 of these scans; progression-free survival was identical for patients with positive interim PET scans and negative biopsy results and those with negative interim PET scans. Therefore, an interim PET scan is not recommended outside of a clinical trial. If it is used, a repeat biopsy of residual masses is necessary before changing the treatment course. Patients who are undergoing induction therapy should undergo evaluation before receiving RT, including all positive studies, after 3 to 4 cycles of chemotherapy. End-of-treatment restaging is performed on completion of treatment. Although the optimal time to end-of-treatment restaging is unknown, the panel recommends waiting 6 to 8 weeks after completion of therapy before repeating PET scans.

**Interim and End-of-Treatment Response Evaluation for Stages I and II:** When the treatment plan involves RT after a short course of chemoimmunotherapy, restaging should be undertaken beforehand, including repeat PET scan, because the dose of RT will be influenced by the result (see Principles of Radiation Therapy, available online, in these guidelines, at www.NCCN.org [NHODG-E]).

If the interim restaging shows a complete response, the planned course of treatment is completed. If the interim restaging shows a partial response, completing the planned course of treatment with a higher dose of RT is appropriate (see Principles of Radiation Therapy, available online, in these guidelines, at www.NCCN.org [NHODG-E]). Alternatively, a repeat biopsy can be obtained and, if positive, the patient can proceed to second-line therapy followed by HDT/ASCR. It is appropriate to enroll patients with an interim partial response in a clinical trial. The choice between these options is often made on clinical grounds. RT is appropriate for patients not eligible for HDT/ASCR. Higher-dose RT is also a reasonable choice in the presence of a very good partial response. Patients with refractory or primarily progressive disease are managed as refractory or relapsed disease.

End-of-treatment restaging is performed on completion of treatment. After end-of-treatment restaging, follow-up at regular intervals is recommended.
for patients with complete response. Patients with a partial response and those with no response to treatment or progressive disease are treated as described for relapsed or refractory disease.

Patients are then followed up at regular intervals (every 3–6 months for 5 years, and then annually or as clinically indicated). Repeat imaging is performed as clinically indicated.

**Interim and End-of-Treatment Response Evaluation for Stages III and IV:** After interim staging, the planned course of treatment (R-CHOP to a total of 6 cycles) is completed for patients with complete and partial responses. End-of-treatment restaging is performed on completion of treatment. Observation is preferred for patients with complete response. RT to initially bulky disease or first-line consolidation with HDT/ASCR can be considered (category 2B). Patients with a partial response and those with no response to treatment or progressive disease are treated as described for relapsed or refractory disease.

### Relapsed or Refractory Disease

The role of HDT/ASCR in patients with relapsed or refractory disease was shown in an international randomized phase III trial (PARMA study). In this study, 109 patients with relapsed or refractory DLBCL responding to first-line chemotherapy were randomized to either chemotherapy plus RT (54 patients) or RT plus HDT/ASCR. At 5 years, the event-free and overall survival rates for the transplant group were 46% and 53%, respectively, compared with 12% and 32% for the nontransplant group.

The efficacy of second-line therapy is predicted by the second-line age-adjusted IPI. Furthermore, pretreatment PET scans have been identified as predictive factors after HDT/ASCR. PET positivity before transplant and chemoresistance are also associated with a poor outcome. The results of the studies from the GEL-TAMO group and Autologous Blood and Bone Marrow Transplant (ABMTR) showed that HDT/ASCR should be considered for patients who never experience a complete remission but are still chemotherapy-sensitive.

Several chemotherapy regimens have been used as second-line therapy before HDT/ASCR. However, none of these has emerged as a preferred regimen. Rituximab as a single agent was modestly active in patients with relapsed or refractory DLBCL and is reserved for frail, elderly patients. In a phase II study, rituximab in combination with ifosfamide, carboplatin, and etoposide (R-ICE) produced a complete response rate of 53% in patients with relapsed or refractory DLBCL, which is significantly better in historical comparison with the response rates observed for these patients treated with ICE alone (27%). In an outpatient setting, R-ICE produced an overall response rate of 71% (25% complete response, and 46% partial response) and an estimated 1-year event-free survival rate of 60% in patients with refractory B-cell lymphoma. Rituximab with other regimens has also been effective in patients with relapsed or refractory DLBCL.

An international Intergroup study (CORAL study) compared R-ICE and DHAP (dexamethasone, cisplatin, and cytarabine; R-DHAP) followed by ASCR in patients with relapsed DLBCL. No significant differences were seen in the 3-year event-free (26% vs. 35%) and overall survival rates (47% vs. 51%) between R-ICE and R-DHAP. However, patients refractory to upfront rituximab-based chemotherapy or those with early relapse have a poor response rate and prognosis. Similar findings were reported in the retrospective analysis conducted by the GEL-TAMO study group.

Lenalidomide is active in heavily pretreated patients with relapsed or refractory DLBCL. In a subset analysis of the NHL-003 study, which evaluated lenalidomide in patients with relapsed or refractory aggressive NHL among 103 patients with DLBCL, an overall response rate of 30% was seen (7% with a complete response and 23% with a partial response). Recent data suggest that the activity of lenalidomide in DLBCL is restricted to the activated B-cell phenotype.

**NCCN Recommendations:** HDT/ASCR is the preferred treatment for patients with relapsed or refractory disease. These patients who are candidates for HDT/ASCR should be treated with second-line chemotherapy with or without rituximab. Suggested regimens (with or without rituximab) include the following:

- DHAP (dexamethasone, cisplatin, and cytarabine)
- ESHAP (methylprednisolone, etoposide, cytarabine, and cisplatin)
- GDP (gemcitabine, dexamethasone, and cisplatin)
- GemOX (gemcitabine and oxaliplatin)
- ICE (ifosfamide, carboplatin, and etoposide)
- MINE (mitoxantrone, ifosfamide, mesna, and etoposide)
Non-Hodgkin's Lymphomas

Patients with a complete or partial response to a second-line chemotherapy regimen should be considered for further consolidation with HDT/ASCR (category 1) with or without RT. IFRT before HDT/ASCR has been shown to result in good local control and an improved outcome. Additional RT can be given before or after stem cell rescue to sites with prior positive disease. Pertinent clinical trials that include the option of ASCR is another option.

Patients who are not eligible for HDT/ASCR should be treated in the context of a clinical trial. Alternatively, they can be treated with single-agent rituximab or lenalidomide (in patients with non-germinal center DLBCL) or multiagent chemotherapy regimens (with or without rituximab), such as dose-adjusted EPOCH, CEPP, GDP, (gemcitabine, dexamethasone, and cisplatin) or GemOx.

Patients with disease relapse after HDT/ASCR should be treated in the context of a clinical trial or individually. However, those with progressive disease after 3 successive regimens are unlikely to derive additional benefit from currently available chemotherapy regimens, except for those with a long disease-free interval.

PMBL

PMBL is a distinct subtype of NHL that can be histologically indistinguishable from DLBCL. It tends to occur in young adults with a median age of 35 years, with a female predominance. PMBL arises from thymic B cells, with initial locoregional spread to supraclavicular, cervical, and hilar nodes and into the mediastinum and lung. Widespread metastatic disease is uncommon at initial diagnosis, but can be more common at recurrence. Clinical symptoms related to rapid growth of mediastinal mass include superior vena cava syndrome, and pericardial and pleural effusions.

Gene expression profiling has indicated that PMBL is distinct from DLBCL; the pattern of gene expression in PMBL is more similar to classical Hodgkin lymphoma. PMBL expresses B-cell antigens and lacks surface immunoglobulins. PMBL is CD19+, CD20+, CD22+, CD21−, IRF4/MUM1+, and CD23+, with variable expression of BCL2 and BCL6. CD30 is weakly and heterogeneously expressed in more than 80% of cases, and CD15 is occasionally present. CD10 positivity is seen in 8% to 32% of cases. PMBL is also characterized by a low expression of human leukocyte antigen class I or II molecules. Rare cases of mediastinal gray zone lymphomas with combined features of PMBL and classical Hodgkin lymphoma have been reported. Cytogenetic and oncogene abnormalities that are common in PMBL include gains in chromosome 9p24 (involving JAK2 in 50%–75% of patients) and chromosome 2p15 (involving c-REL, encoding a member of the NF-kB family of transcription factors), and losses in chromosomes 1p, 3p, 13q, 15q, and 17p.

The IPI is of limited value in determining the prognosis of PMBL at diagnosis. In a retrospective analysis of 141 patients from MSKCC, 2 or more extranodal sites and initial therapy received were predictors of event-free survival, whereas only the initial therapy received was a predictor for overall survival.

In retrospective analyses, intensive chemotherapy regimens have been more effective than CHOP, and the addition of IFRT improved outcomes. The role of RT must be confirmed in randomized trials. In a retrospective study, the addition of rituximab to MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin) or VACOP-B (etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin) did not seem to result in significant differences in clinical outcomes. Larger studies are needed to confirm this, especially in light of 2 different studies reporting that the addition of rituximab to CHOP plus RT or dose-adjusted EPOCH without RT improved response rates and event-free survival rates. Sequential dose-dense R-CHOP followed by ICE consolidation (without RT) was also highly effective in patients with PMBL. At a median follow-up for surviving patients at 3 years, the overall and progression-free survival rates were 88% and 78%, respectively.

However, in the absence of randomized trials, no optimal treatment has been established for patients with PMBL. R-CHOP-21 is widely used at NCCN Member Institutions based on data in DLBCL. PET-CT is essential posttreatment. If PET-CT is negative at the end of treatment, patients may be observed. Residual mediastinal masses are common. If PET-CT is positive, biopsy is recommended if additional treatment is contemplated.
Cutaneous B-Cell Lymphomas

Cutaneous B-cell lymphomas (CBCLs) are a group of B-cell lymphomas originating in and usually confined to the skin. CBCLs are estimated to represent approximately 20% to 25% of all primary cutaneous lymphomas. In the United States, the SEER data from the NCI indicated that the incidence of cutaneous T-cell lymphomas accounted for 71%, whereas CBCLs accounted for 29% from 2001 to 2005. The new WHO-EORTC classification for cutaneous lymphomas distinguishes 3 main types of CBCL:

- Primary cutaneous marginal zone B-cell lymphoma (PCMZL)
- PCFCL
- PCDLBCL-LT

PCFCL is the most common type of CBCL, whereas PCDLBCL-LT is rare. PCMZL and PCFCL are indolent or slow-growing, whereas PCDLBCL-LT is an aggressive lymphoma with a generally poorer prognosis. In an Italian series of 467 patients with CBCL, PCFCL and PCMZL accounted for 57% and 31% of cases, respectively. PCDLBCL-LT was reported in only 11% of patients. Although the various types of CBCL can occur anywhere on the skin, PCFCL is more prevalent on the scalp and forehead, whereas the trunk and extremities are the most common sites for PCMZL. The leg remains the most common site for PCDLBCL. Extracutaneous involvement is more frequent with PCDLBCL-LT. In the same large Italian series, extracutaneous involvement eventually developed in 6% of patients with PCMZL, 11% with PCFCL, and 17% with PCDLBCL-LT. In patients with PCMZL and PCFCL, patients with single lesions had higher disease-free and overall survival rates than those with regional or disseminated lesions (62% vs. 44% and 97% vs. 85%, respectively), whereas in patients with PCDLBCL-LT the differences were only of borderline significance (55% vs. 44% and 79% vs. 67%, respectively). In another series of 145 patients with CBCL, Grange et al. also identified locations on the leg and multiple skin lesions as independent poor prognostic factors for patients with CBCLs.

Diagnosis

Adequate biopsy of the lesions should be obtained and the slides reviewed by a pathologist with expertise in the diagnosis of primary CBCLs (PCBCLs). Incisional, excisional, or punch biopsy is preferred to shave biopsy, because CBCLs have primarily dermal infiltrates, often deep, which are less well sampled and can even be missed with a shave biopsy. Adequate immunophenotyping with a panel that evaluates B- and T-cell markers is recommended to establish the diagnosis of the exact subtype of CBCL. The panel should include CD20, CD79a, CD3, CD5, CD10, BCL2, BCL6, Ki-67, kappa/lambda, and IRF4/MUM1. PCFCL is consistently BCL6+, whereas CD10 and BCL2 are expressed in only a few cases with a follicular growth pattern. PCMZLs are always negative for BCL6 and CD10, but are often BCL2+.

Although the diagnosis of PCMZL is generally straightforward and reproducible among pathologists, it is more difficult to distinguish from PCFCL and PCDLBCL-LT. Part of the difficulty is that cell size (large vs. small) is not a defining feature like it is in nodal B-cell lymphomas. Most of the patients with PCFCL have lesions with a germinal center phenotype, whereas most with PCDLBCL-LT have an activated B-cell phenotype. In nodal DLBCL, the germinal center phenotype is associated with a better prognosis than the activated B-cell phenotype. Both PCFCL and PCDLBCL are CD20+ and BCL6+. BCL2 is usually negative in PCFCL but highly expressed in PCDLBCL-LT. In addition, PCFCL is usually MUM/IRF4+, whereas PCDLBCL-LT is usually IRF4/MUM1+ and shows strong expression of FOXP1. IRF4/MUM1 and FOXP1 may serve as additional diagnostic markers in the differential diagnosis of PCFCL and PCDLBCL. Assessment of surface IgM and IgD expression may be helpful in distinguishing PCDLBCL-LT from PCFCL.

The t(14;18) translocation occurs only rarely in PCBCLs. Therefore, detection of a t(14;18) translocation in CBCL suggests the presence of systemic disease. Molecular genetic analysis to detect TCR gene rearrangements, PCR to detect IGHV rearrangements, and cytogenetics or FISH to detect t(14;18) may be useful in selected circumstances. In selected cases, the use of cyclin D1 may be useful to differentiate PCMZL (negative for CD5 and cyclin D1) from MCL (positive for CD5 and cyclin D1). MCL is not a primary cutaneous lymphoma, and finding it in the skin requires a careful search for extracutaneous disease.
Workup

Initial workup is geared toward evaluating extent of disease on the skin and seeking extracutaneous disease. The absence of extracutaneous disease at diagnosis is part of the definition of PCBCL. The initial workup includes a complete physical examination, comprehensive skin examination, and CT scans of the chest, abdomen, and pelvis. PET-CT may have higher sensitivity in finding otherwise occult systemic disease, but this is not validated and the higher rates of false-positive findings can create confusion. Bone marrow biopsy is essential for PCDLBCL-LT, whereas its role is unclear for PCFCL and PCMZL. Senff et al.\textsuperscript{30} evaluated 275 patients with histologic features consistent with MZL (n = 82) or FCL (n = 193) first presenting in the skin.\textsuperscript{30} Bone marrow involvement was seen in approximately 11% of patients in the FCL group compared with less than 1% in the MZL group. Patients with follicle center lymphoma (FCL) and skin lesions and positive bone marrow biopsy results had a significantly worse prognosis than those with PCFCL. The 5-year overall survival rate was 44% and 84%, respectively.

The International Society of Cutaneous Lymphomas (ISCL) and the EORTC task force recommend that bone marrow biopsy be required for cutaneous lymphomas with intermediate to aggressive behaviors, and should be considered for cutaneous lymphomas with indolent behavior in the presence of any evidence of extracutaneous disease, as indicated by other staging assessments (e.g., radiographic evidence or serologic clues, such as elevated monoclonal or polyclonal immunoglobulins).\textsuperscript{29} The guidelines recommend considering bone marrow biopsy for patients with PCFCL. It is optional for patients with PCMZL. Peripheral blood flow cytometry will be useful in selected cases when CBC shows lymphocytosis.

Treatment

Primary CBCLs have a different clinical course and prognosis that distinguish them from their nodal counterparts. Treatment options for CBCLs depend on the histology and stage of the disease. Most commonly used therapies include excision, RT, rituximab, or systemic chemotherapy.\textsuperscript{559,360}

In a large retrospective analysis by the Italian Study Group for Cutaneous Lymphomas involving 467 patients with PCBCL, the complete response, 5-year overall survival, and 10-year overall survival rates for all patients with PCFCL and PCMZL who received treatment were 90%, 96%, and 90%, respectively.\textsuperscript{361} The relapse rate was 44% and extracutaneous spread was observed in 6% to 11% of patients. Relapse rate did not vary by type of initial therapy.

In patients with PCDLBCL-LT, the complete response, 5-year overall survival, and 10-year overall survival rates were 82%, 73%, and 47%, respectively. PCDLBCL-LT is also associated with higher relapse rates (55%) and incidences of extracutaneous spread (17%). Higher relapse rates were confirmed for patients with single or regional lesions treated with RT and those with disseminated cutaneous involvement treated with chemotherapy as first-line treatment.

RT is very effective when used as initial local therapy and for cutaneous relapses in most patients with indolent CBCLs.\textsuperscript{370-372} In patients with indolent histologies, RT and excision were associated with higher response rates than chemotherapy (96%, 97%, and 79%, respectively) but are generally used for those with more limited disease.\textsuperscript{363} However, most patients with regional or disseminated disease will experience relapse after any type of treatment. Relapses are generally confined to the skin.

In a retrospective of 34 patients with CBCL treated with RT, the 5-year relapse-free survival rate ranged from 62% to 73% for PCFCL and PCMZL but was only 33% for PCDLBCL-LT.\textsuperscript{372} Five-year overall survival was 100% for PCFCL and PCMZL but was 67% for PCDLBCL-LT. Senff et al.\textsuperscript{371} evaluated the outcome of 153 patients with CBCL (25 with PCMZL, 101 with PCFCL, and 27 with PCDLBCL) who were initially treated with RT with a curative intent. Overall, 45% of patients had single lesions, and localized or disseminated lesions were seen in 43% and 12% of patients, respectively. Complete remission was experienced by 151 of 153 patients (99%). Relapse rates for PCMZL, PCFCL, and PCDLBCL-LT were 60%, 29%, and 64%, and the 5-year disease-specific survival rates were 95%, 97%, and 59%, respectively. The PCFCLs presenting on the legs had a higher relapse rate (63%) and a lower 5-year disease-specific survival rate (44%) than PCFCLs at other sites (25% and 99%, respectively).\textsuperscript{371}

Thus, local therapy is suitable for patients with indolent histologies, whereas patients with PCDLBCL-LT, which has a more unfavorable clinical course, are generally treated with more aggressive treatment modalities, often combined modality therapy.\textsuperscript{373}
Non-Hodgkin’s Lymphomas

NCCN Recommendations

Because of the lack of data from randomized clinical trials, the treatment recommendations included in the NCCN Guidelines are derived from the management of patients with CBCL at NCCN Member Institutions based on the limited data from retrospective analyses and studies involving small cohorts of patients.

PCFCL and PCMZL: Initial Treatment: The guidelines recommend local RT or excision as the initial treatment options for patients with solitary lesions or regional disease (T1–2). Selected patients with local disease that is not amenable to local therapy (e.g., lesions on the scalp or forehead) can be observed.

For patients presenting with generalized skin lesions (T3), several treatment options are available. Chlorambucil has been shown to be effective in the treatment of PCMZL with multifocal skin lesions.\(^\text{374}\) In patients presenting with PCFCL, multiagent chemotherapy and RT were equally effective for multifocal skin lesions.\(^\text{375–377}\) Rituximab has been effective as a first-line treatment option for patients with indolent CBCLs with multiple lesions for which local therapy is not effective.\(^\text{378–382}\) In a series of 16 patients with PCBCL, 14 patients (87.5%) experienced complete remission, with 35% of these patients experiencing relapse between 6 and 37 months.\(^\text{382}\) In another retrospective analysis of 15 patients with indolent CBCLs, the overall objective response rate was 87% (60% with a complete response, 27% with a partial response) with a median follow-up of 36 months.\(^\text{381}\) The overall response rate was 100% for patients with PCFCL and 60% for those with PCMZL. Median time to response, duration of response, and time to progression were 30 days, 24 months, and 24 months, respectively. There are case reports showing the efficacy of topical therapy with using steroids, imiquimod, and nitrogen mustard or bexarotene gel.\(^\text{375,383–386}\)

For patients presenting with generalized disease, the guidelines have included observation, rituximab, topical therapy, local RT, intralesional steroids, or systemic therapy (chlorambucil or CVP) with or without rituximab as options. In patients with very extensive or symptomatic disease, other chemotherapy regimens recommended for the treatment of FL may be used.

Patients presenting with extracutaneous disease should be managed according to the FL guidelines.

Treatment for Relapsed or Refractory Disease: Although most patients respond to initial therapy, relapses do commonly occur. Patients with regional or localized relapse should undergo additional therapy (excision, intralesional steroids, local RT, or topical therapy using steroids, imiquimod, nitrogen mustard, or bexarotene gel), and those with generalized disease relapse confined to the skin should undergo additional therapy with treatment options recommended for generalized disease at presentation.

Patients with a partial response or persistent progressive disease after additional treatment should be treated with the other options included in the initial treatment to improve response before starting treatment for refractory disease. Patients with extracutaneous or cutaneous relapse that is not responding to any of the initial treatment options should be managed according to the FL guidelines.

PCDLBCL-LT: Initial Treatment: PCDLBCL-LT has a poorer prognosis than other CBCL, particularly in patients with multiple tumors on the legs. RT alone is less-often effective in patients with PCDLBCL. Although these lesions do respond to radiation, remissions are often short-lived, and higher rates of dissemination to extracutaneous sites occur. In a retrospective multicenter study from the French Study Group on 60 patients with PCDLBCL-LT, although no particular therapy (RT or multiagent chemotherapy with or without rituximab) was significantly associated with improved survival, patients treated with anthracycline-containing chemotherapy and rituximab had a more favorable short-term outcome.\(^\text{362}\) Among 12 patients treated with anthracycline-based chemotherapy with rituximab, the complete response rate was 92% compared with 62% among those who underwent other therapies. The 2-year survival rates for these groups were 81% and 59%, respectively.

For patients with localized disease, the NCCN Guidelines recommend local RT alone or in combination with R-CHOP. RT alone can be used in elderly patients or those unable to tolerate systemic therapy. In patients with generalized disease, R-CHOP with or without RT is recommended. Extracutaneous disease should be managed according to the DLBCL guidelines. The guidelines recommend enrollment in clinical trials for all patients with PCDLBCL-LT.

Treatment for Relapsed or Refractory Disease: In patients with regional relapses, R-CHOP is recommended if
they have not received prior chemotherapy. Patients who have received prior chemotherapy should be treated with local RT or second-line chemotherapy regimens recommended for relapsed or refractory DLBCL. Local RT or second-line chemotherapy regimens are options for patients with generalized relapse. In a pilot study of 10 patients, radioimmunotherapy with yttrium 90Y ibritumomab tiuxetan was effective in patients with relapsed CBCLs. The guidelines have included radioimmunotherapy as one of the treatment options for patients with relapsed disease.

References

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The NCCN Guidelines Panel for Non-Hodgkin’s Lymphomas has no conflicts to disclose.