Primary Cutaneous B-Cell Lymphomas

**DIAGNOSIS**

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

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

**WORKUP**

**ESSENTIAL:**
- History and physical exam, including complete skin exam
- CBC, differential, comprehensive metabolic panel
- LDH
- Hepatitis B testing if rituximab considered
- Contrast-enhanced chest/abdominal/pelvic CT and/or PET-CT scan
- Bone marrow biopsy, if PC-DLBCL, Leg type
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

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

**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.

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

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

Typical immunophenotype: PC-DLBCL: CD20+ BCL2+ CD10- BCL6/- IRF4/MUM1+/- ; PCFCL: CD20+ BCL2- CD10+/- BCL6+ IRF4/MUM1-; PCMZL: CD20+ BCL2+/- CD10- BCL6- IRF4/MUM1+/- cytoplasmic kappa+ or lambda+ in about 40%.

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

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

---

dRule out drug-induced cutaneous lymphoid hyperplasia.

eHepatitis 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.
Primary Cutaneous B-Cell Lymphomas

**Primary Cutaneous Marginal Zone Lymphoma or Follicle Center Lymphoma**

**Stage**

- **Solitary/regional, T1-2 (Ann Arbor Stage IE)**
  - Local RT (preferred) and/or Excision
  - In selected cases: Observation or Topicals or Intrallesional steroids

- **Generalized disease (skin only), T3**
  - Observation or Topicals or Local RT for symptoms or Intrallesional steroids or Rituximab or Other systemic therapy

**Extracutaneous disease**

- Manage as per FOLL-3

**Initial Therapy**

- Response ➔ Observe ➔ Relapsed or progressive disease ➔ Local RT is the preferred initial treatment, but not necessarily the preferred treatment for relapse.

- Regional
- Generalized disease (extracutaneous disease)
- Generalized disease (skin only)

- Refractory disease ➔ Treat with alternate initial therapy

- Generalized disease (skin only)

- Manage as per FOLL-3

**Note:**
All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type

**Stage**

<table>
<thead>
<tr>
<th>Initial Therapy</th>
<th>Secondary Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Solitary regional, T1-2 (Ann Arbor Stage IE)</strong></td>
<td></td>
</tr>
<tr>
<td>RCHOP(^n) + local RT or Local RT(^o) or Clinical trial</td>
<td></td>
</tr>
<tr>
<td>CR → Observe → Relapse</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>RCHOP (if not previously received) or Manage as per BCEL-6 or Local RT to previously unirradiated tumor</td>
<td></td>
</tr>
</tbody>
</table>

| **Generalized disease (skin only), T3** |
| RCHOP\(^n\) ± local RT or Clinical trial |
| CR → Observe → Relapse |
| PR |
| Manage as per BCEL-6 or Local RT for palliation or Radioimmunotherapy |

| **Extracutaneous disease** |
| Manage as per BCEL-3 |

---

\(^n\)See TNM Classification of Cutaneous Lymphoma other than MF/SS (CUTB-A).

\(^o\)For patients who cannot tolerate anthracyclines, see BCEL-C for regimens for patients with poor left ventricular function.

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

---

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
TNM CLASSIFICATION OF CUTANEOUS LYMPHOMA OTHER THAN MF/SS\(^{a,b}\)

<table>
<thead>
<tr>
<th>T</th>
<th>Solitary skin involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>a solitary lesion &lt;5 cm diameter</td>
</tr>
<tr>
<td>T1a</td>
<td>a solitary lesion &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(^b)</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(^b)</td>
</tr>
<tr>
<td>T3b</td>
<td>multiple lesions involving ≥3 body regions(^b)</td>
</tr>
<tr>
<td>N</td>
<td>No clinical or pathologic lymph node involvement</td>
</tr>
<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(^c) 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(^c) 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>
</tr>
<tr>
<td>M</td>
<td>No evidence of extracutaneous non-lymph node disease</td>
</tr>
<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>

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

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

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

---

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
BODY REGIONS FOR THE DESIGNATION OF T (SKIN INVOLVEMENT) CATEGORY\textsuperscript{a,b,c}

\begin{itemize}
    \item Head and neck: inferior border—superior border of clavicles, T1 spinous process.
    \item Chest: superior border—superior border of clavicles; inferior border—inferior margin of rib cage.
    \item Abdomen/genital: superior border—inferior margin of rib cage; inferior border—inguinal folds, anterior perineum.
    \item Upper back: superior border—T1 spinous process; inferior border—inferior margin of rib cage.
\end{itemize}

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

\textsuperscript{b}Left and right extremities are assessed as separate body regions. The designation of these body regions are based on regional lymph node drainage patterns.

Primary Cutaneous B-Cell Lymphomas

**TREATMENT REFERENCES**

**Rituximab**

**Chemotherapy**

**Topicals**

**Topical nitrogen mustard**

**Topical bexarotene**

**Topical imiquimod**

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