NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

T-cell Lymphomas

Version 2.2017 — February 21, 2017
Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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

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

See NCCN Categories of Evidence and Consensus.

NCCN T-Cell Lymphomas Panel Members
Summary of the Guidelines Updates

- Peripheral T-Cell Lymphomas (TCEL-1)
- Breast Implant-Associated ALCL (BIAA-1)
- Mycosis Fungoides/Sezary Syndrome (MFSS-1)
- Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders (PCTLD-1)
- T-Cell Large Granular Lymphocytic Leukemia (LGLL-1)
- Adult T-Cell Leukemia/Lymphoma (ATLL-1)
- T-Cell Prolymphocytic Leukemia (TPLL-1)
- Extranodal NK/T-Cell Lymphoma, nasal type (NKTL-1)

- Supportive Care (LYMP-A)
- Lugano Response Criteria for Non-Hodgkin’s Lymphoma (LYMP-B)
- Principles of Radiation Therapy (LYMP-C)

Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (See NCCN Guidelines for B-Cell Lymphomas)

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Updates in Version 2.2017 of the NCCN Guidelines for T-Cell Lymphomas from Version 1.2017 include:

**MFSS-A 1 of 4**

- **Systemic therapies, Category B**
  - Second-line therapies, "pembrolizumab" was added with a category 2B designation. Corresponding footnote "g" was added, "Pembrolizumab (K025701) for treatment of relapsed/refractory mycosis fungoides and Sezary syndrome: Clinical efficacy in a CITN multicenter phase 2 study [abstract]. Blood 2016;125:Abstract 181."

Updates in Version 1.2017 of the NCCN Guidelines for T-Cell Lymphomas from Version 3.2016 include:

- **MFSS-A 1 of 4**
  - **Systemic therapies, Category B**
    - Second-line therapies, "pembrolizumab" was added with a category 2B designation. Corresponding footnote "g" was added, "Pembrolizumab (K025701) for treatment of relapsed/refractory mycosis fungoides and Sezary syndrome: Clinical efficacy in a CITN multicenter phase 2 study [abstract]. Blood 2016;125:Abstract 181."

**New Algorithm**

**BIAA-1**

- A new algorithm for "Breast Implant-Associated ALCL" was added to the Guidelines.

**Global changes**

- The new 2016 WHO classification of the Mature B-Cell, T-Cell, and NK-Cell Neoplasms was added.
- Suggested treatment regimen references were updated throughout the guidelines.
- Workup, bullet was revised, "Pregnancy testing in women of child-bearing age (if chemotherapy or RT planned)"
- Workup, bullet was revised, "MUGA scan/Echocardiogram or MUGA scan if anthracycline or anthracenedione-based regimen is indicated."
- For imaging with CT, "C/A/P" was added for "chest/abdominal/pelvic" and "with contrast" was added as appropriate throughout the Guidelines.

**Peripheral T-Cell Lymphomas**

**TCEL-1**

- Diagnosis, Useful Under Certain Circumstances
  - 2nd bullet was added, "DUSP22 rearrangement for ALCL, ALK negative"
- Subtypes
  - "Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)" was added with footnote f, "MEITL has only recently been separated as its own entity and optimal treatment has not been defined." (Also for other TCEL pages)

**TCEL-3**

- Footnote i was added, "ALK-, ALK-negative with a DUSP22 rearrangement has been associated with a prognosis more similar to ALK-positive disease and could be treated according to the ALCL-, ALK-positive algorithm. (Parrilla Castellar ER, Jaffe ES, Said JW, et al. ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes. Blood 2014;124:1473-1480.)" Also for TCEL-B 1 of 5.

**TCEL-B 3 of 5**

- Second-line and Subsequent Therapy
  - "Brentuximab vedotin for CD30+AITL" was added for both with intention and no intention to transplant.
Updates in Version 1.2017 of the NCCN Guidelines for T-Cell Lymphomas from Version 3.2016 include:

**Mycosis Fungoides/Sezary Syndrome**

**General**
- For response to therapy
  - Refractory disease was revised by adding, "to multiple previous therapies" from the previous footnote, “Refractory or intolerant to multiple previous therapies.” on all appropriate pages.

**MFSS-1**
- Diagnosis, IHC panel of skin biopsy was moved from Useful to Essential.

**MFSS-2**
- Imaging studies, 1st sub-bullet was revised by adding, "arms/legs included when disease assessment of entire body is needed" whole body PET/CT

**MFSS-3**
- TNMB classification for blood, B0, B1, and B2 were all revised.
- Footnote k was revised, "Sezary syndrome is defined by B2 blood involvement and as a clonal rearrangement of the TCR in the blood (clones should be relevant to clone in the skin) and either ≥1000/mcL or increased CD4 or CD3 cells with CD4/CD8 of ≥10 or increase in CD4 cells with an abnormal phenotype (≥40% CD4+/CD7- or ≥30% CD4+/CD26- of the total lymphocyte count)."

**MFSS-6**
- Footnote t was added, "Imaging indicated when suspicious of clinical extracutaneous disease with modalities used in workup."

**MFSS-7**
- After Stage II B, the two options were revised,  
  - Limited extent tumor lesions ± patch/plaque disease 
  - Generalized extent tumor lesions transformed, and/or folliculotropic disease

- Footnotes  
  - Footnote t was added, "Imaging indicated when suspicious of clinical extracutaneous disease with modalities used in workup." (Also for MFSS-8)
  - Footnote was removed, "For non-radiated sites, see Stage I-IIA. After patient is rendered disease free by RT, may consider adjuvant systemic biologic therapy (SYST-CAT A) after RT to improve response duration."

**MFSS-8**
- Footnote ee was revised, "Generalized skin-directed therapies (other than topical steroids) TSEBT may not be well-tolerated in stage III and should be used with caution. Phototherapy (PUVA or UVB) or TSEBT can be used successfully. In selected cases, TSEBT may be used with lower doses and slower fractionation."

**MFSS-9**
- Sezary syndrome
  - For primary treatment, a new imaging footnote kk was added, "If disease in lymph nodes and/or viscera or suspicious of disease progression, imaging with modalities used in workup as clinically indicated based on distribution of disease."
  - After relapse or persistent disease,
    - Alemuruzumab was added.
    - Clinical trial was added.
  - Non Sezary or visceral disease
  - After primary treatment, "Repeat imaging with modalities used in workup (frequency as clinically indicated)" was added.
  - After relapse or persistent disease,
    - Clinical trial was added.

**MFSS-A 1 of 4**
- Skin-directed therapies
  - For generalized skin involvement, 4th bullet,
    - Qualifier statement was removed from TSEBT, "reserved for those with severe skin symptoms or generalized thick plaque or tumor disease, or poor response to other therapies."

**MFSS-B**
- Supportive Care for MF/SS
  - Statement was added, "Collaboration with dermatologist for supportive care is essential."
  - Pruritus, Treatment
    - Qualifier statement was removed from TSEBT, "reserved for those with severe skin symptoms or generalized thick plaque or tumor disease, or poor response to other therapies."

- Infections, Prophylaxis
  - 3rd sub-bullet was revised by adding,
    - Diluted bleach baths or soaks (if limited area): Either 2 teaspoons of bleach in 1 gallon of water OR 1 quarter of a cup (NOT 1 cup) of bleach in a bathtub of water

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NCCN Guidelines Version 2.2017 Updates
T-Cell Lymphomas

Updates in Version 1.2017 of the NCCN Guidelines for T-Cell Lymphomas from Version 3.2016 include:

**Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders**

**PCTLD-2**
- Diagnosis, Essential
  - Useful under certain circumstances
    - On skin biopsy, 1st sub-bullet was revised by adding, "MUM1, FISH 6p25.3, EMA."
    - Footnote g was revised, "Typical immunophenotype: CD30+ (>70-75% cells)"

**PCTLD-4**
- Primary cutaneous ALCL, multifocal lesions
  - Interferon alpha was added as a primary treatment option with a category 3 designation.

**T-Cell Large Granular Lymphocytic Leukemia**

**LGLL-1**
- Diagnosis, Essential
  - 4th bullet, IHC, "perforin" was added.
  - Granzyme M and EBER-ISH were moved to Useful Under Certain Circumstances.
  - Molecular analysis to detect gene rearrangement was moved from Essential to Useful
- Workup, Essential
  - Bullet was added, "Pregnancy testing in women of child-bearing age (if chemotherapy or RT planned)." (Also for TPLL-1)

**Adult T-Cell Leukemia/Lymphoma**

**ATLL-2**
- Footnote I was added, "If nodal disease is present, repeat C/A/P CT with contrast or PET/CT." Also for ATLL-3.

**ATLL-B**
- Suggested treatment regimens were added for "Second-line Therapy (with intention to proceed to HDT/ASCR) or Subsequent Therapy to HDT/ASCR." Hyperlinks to these regimens were added to ATLL-3.

**Extranodal NK/T-Cell Lymphoma, nasal type**

**NKTL-2**
- Footnote a was added, "It is preferred that treatment occur at centers with expertise in the management of this disease." (Also for NKTL-3)

**NKTL-A**
- "NK/T-Cell Lymphoma Prognostic Index" was replaced with the "Prognostic Index of Natural Killer Lymphoma (PINK)" and "Prognostic Index of Natural Killer Lymphoma with Epstein-Barr Virus DNA (PINK-E)." The index was updated in workup section on NKTL-1.

**NKTL-B 1 of 2**
- Radiation therapy alone, "unfit for chemotherapy" was added.

**Supportive Care**

**LYMP-A 1 of 2**
- Footnote a was added. "There are data to support that fixed dose rasburicase is very effective in adult patients."

**Principles of Radiation Therapy**

**LYMP-C 3 of 4**
- NK-T cell lymphoma
  - Dose for RT as primary treatment was modified, 60–65 50–55 Gy
  - Dose for RT in combined modality therapy was modified, 45–60 45–50.4 Gy
DIAGNOSIS

ESSENTIAL:
- Review of all slides with at least one paraffin block representative of the tumor should be done by a hematopathologist with expertise in the diagnosis of PTCL. Rebiopsy if consult material is nondiagnostic.
- An FNA alone is not sufficient for the initial diagnosis of peripheral T-cell lymphoma.
- Adequate immunophenotyping to establish diagnosis
  - IHC panel: CD20, CD3, CD10, BCL6, Ki-67, CD5, CD30, CD2, CD4, CD8, CD7, CD56, CD57, CD21, CD23, EBER-ISH, ALK with or without
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD3, CD5, CD19, CD10, CD20, CD30, CD4, CD8, CD7, CD2; TCRαβ; TCRγ

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- Molecular analysis to detect: antigen receptor gene rearrangements; t(2;5) and variants
- DUSP22 rearrangement for ALCL, ALK negative
- Additional immunohistochemical studies to establish lymphoma subtype: BF1, TCR-CγM1, PD1/CD279, CXCL-13
- Karyotype to establish clonality
- Assessment of HTLV-1 serology in at-risk populations. HTLV-1 PCR if serology is indeterminate.

SUBTYPES

Subtypes included:
- Peripheral T-cell lymphoma (PTCL), NOS
- Angioimmunoblastic T-cell lymphoma (AITL)
- Anaplastic large cell lymphoma (ALCL), ALK positive
- ALCL, ALK negative
- Enteropathy-associated T-cell lymphoma (EATL)
- Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)

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

Extranodal NK/T-cell lymphoma, nasal type

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a See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (See B-cell Lymphomas Guidelines)
b T-cell receptor rearrangements alone are not sufficient for diagnosis, as these are often seen with reactive/inflammatory processes.
c See map for prevalence of HTLV-1 by geographic region.
d Primary cutaneous peripheral T-cell lymphomas are very heterogeneous and the optimal management may not be along these guidelines.
e AITL may occasionally present with concurrent DLBCL. EBV and appropriate immunohistochemistry should be performed.
f MEITL has only recently been separated as its own entity and optimal treatment has not been defined.

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

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

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

The role of intrathecal prophylaxis in PTCL is largely unknown.

See International Prognostic Index (TCEL-A).
**ALCL, ALK positive**

Stage I, II →

- Multiagent chemotherapy\(^k\) x 6 cycles ± ISRT (30–40 Gy)
- Multiagent chemotherapy\(^k\) x 3–4 cycles + ISRT (30–40 Gy)

Stage III, IV →

Multiagent chemotherapy\(^k\) x 6 cycles

**Relapse, See Additional Therapy (TCEL-4)**

**Stage I, II**

- Clinical trial (preferred)
- Multiagent chemotherapy\(^k\) x 6 cycles ± ISRT (30–40 Gy)

**Stage I–IV**

- PTCL, NOS
- ALCL, ALK negative
-AITL
- EATL
- MEITL

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

**Complete response**

- Clinical trial or Consider high-dose therapy with stem cell rescue
- Observe

**Partial response or no response or progressive disease**

- Clinical trial or Observe

**Relapse, See Additional Therapy (TCEL-4)**

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\(^1\)MEITL has only recently been separated as its own entity and optimal treatment has not been defined.

\(^2\)ALK−, ALK-negative with a DUSP22 rearrangement has been associated with a prognosis more similar to ALK-positive disease and could be treated according to the ALCL−, ALK-positive algorithm. (Parrilla Castellar ER, Jaffe ES, Said JW, et al. ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes. Blood 2014;124:1473-1480.)

\(^3\)For selected patients (elderly, comorbid conditions), a trial of single-agent corticosteroid may be considered for symptom management.

\(^4\)See Suggested Treatment Regimens (TCEL-B).


\(^6\)Localized areas can be irradiated before or after high-dose therapy.

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Relapse/refractory disease

**RELPASE/REFRACTORY DISEASE**

For patients with intention to proceed to transplant

- Consider prophylaxis for tumor lysis syndrome (See LYMPH-A)
- See monoclonal antibody and viral reactivation (LYMPH-A)

No intention to transplant

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

**ADDITIONAL THERAPY**

Complete response or Partial response

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

No response

- Clinical trial or Alternative second-line therapy (See TCEL-B) Best supportive care or Palliative RT

**CONSOLIDATION/ADDITIONAL THERAPY**

RELAPSE #2 OR GREATER

Relapse/refractory disease

- For patients with intention to proceed to transplant
  - Clinical trial (preferred) or Second-line therapy See Suggested Regimens (TCEL-B)

- No intention to transplant
  - Clinical trial or Second-line therapy See Suggested Regimens (TCEL-B) or Palliative RT

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1See Lugano Response Criteria for Non-Hodgkin’s Lymphoma (LYMP-B).

mLocalized areas can be irradiated before or after high-dose therapy.

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### INTERNATIONAL PROGNOSTIC INDEX

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<td>Performance status 2–4</td>
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<td>Stage III or IV</td>
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### PROGNOSTIC INDEX FOR PTCL-U (PIT)

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### AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX

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<tr>
<td>Extranodal involvement &gt; 1 site</td>
<td>High</td>
<td>3</td>
</tr>
</tbody>
</table>

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SUGGESTED TREATMENT REGIMENSa

First-line Therapy:
• Clinical trialb
• ALCL, ALK+ histology
  › CHOP-21 (cyclophosphamide, doxorubicin, vincristine, prednisone)
  › CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone)
• Other histologies (ALCL, ALK-;c PTCL, NOS; AITL; EATL; MEITLd), regimens that can be used include:
  › Preferred regimens (in alphabetical order)
    ◊ CHOEP
    ◊ CHOP-14
    ◊ CHOP-21
    ◊ Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
  › Alternative regimens (in alphabetical order)
    ◊ CHOP followed by IVE (ifosfamide, etoposide, epirubicin) alternating with intermediate-dose methotrexate [Newcastle Regimen] [studied only in patients with EATL]e
    ◊ HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with high-dose methotrexate and cytarabine

First-line Consolidation:
• Consider consolidation with high-dose therapy and stem cell rescue.

Patients with low IPI ALCL, ALK + disease in remission do not need consolidative transplant.

See Second-line and Subsequent Therapy:
• PTCL-NOS and EATL (TCEL-B 2 of 5)
• AITL (TCEL-B 3 of 5)
• ALCL (TCEL-B 4 of 5)

a See references for regimens TCEL-B 5 of 5.
b While CHOP-21 and CHOEIP regimens confer a favorable prognosis in ALCL, ALK +, these regimens have not provided the same favorable results for other PTCL histologies; clinical trial is therefore preferred for the management of these other histologies.
c ALCL-, ALK-negative with a DUSP22 rearrangement has been associated with a prognosis more similar to ALK-positive disease and could be treated according to the ALCL-, ALK-positive algorithm. (Parrilla Castellar ER, Jaffe ES, Said JW, et al. ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes. Blood 2014;124:1473-1480.)
d MEITL has only recently been separated as its own entity and optimal treatment has not been defined.
e CHOP followed by IVE regimen includes HSCT.
SUGGESTED TREATMENT REGIMENS FOR PTCL-NOS, EATL, AND MEITL\textsuperscript{a,d}

**Second-line Therapy (with intention to proceed to transplant) and Subsequent Therapy**
- Clinical trial preferred
- Preferred single agents/combination regimens
  - Single agents (alphabetical order)
    - Belinostat
    - Brentuximab vedotin for CD30+ PTCL
    - Pralatrexate
    - Romidepsin
  - Combination regimens (alphabetical order)
    - DHAP (dexamethasone, cisplatin, cytarabine)
    - ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)
    - GDP (gemcitabine, dexamethasone, cisplatin)
    - GemOx (gemcitabine, oxaliplatin)
    - ICE (ifosfamide, carboplatin, etoposide)

**Alternative Regimens**
- Single agents (alphabetical order)
  - Bendamustine
  - Gemcitabine
  - Lenalidomide
- Combination regimen
  - GVD (gemcitabine, vinorelbine, liposomal doxorubicin)\textsuperscript{f}

\textsuperscript{a}See references for regimens **TCEL-B 5 of 5**.
\textsuperscript{d}MEITL has only recently been separated as its own entity and optimal treatment has not been defined.
\textsuperscript{f}Data suggest there may be excessive pulmonary toxicity with GVD (gemcitabine, vinorelbine, liposomal doxorubicin) regimen when used in combination with unconjugated anti-CD30 monoclonal antibodies for the treatment of Hodgkin lymphoma (Blum KA, Jung SH, Johnson JL, et al. Ann Oncol 2010;21:2246-2254). A similar regimen, gemcitabine and liposomal doxorubicin, may be used for mature T-cell lymphoma; however, it is recommended to wait 3–4 weeks following treatment with brentuximab vedotin before initiation.

**Second-line Therapy (no intention to transplant) and Subsequent Therapy:**
- Clinical trial preferred
- Preferred single agents (alphabetical order)
  - Belinostat
  - Brentuximab vedotin for CD30+ PTCL
  - Pralatrexate
  - Romidepsin
- Alternative single agents (alphabetical order)
  - Alemtuzumab
  - Bendamustine
  - Bortezomib\textsuperscript{g} (category 2B)
  - Gemcitabine
  - Lenalidomide
  - Radiation therapy

See First-line Therapy on **TCEL-B 1 of 5**.

See Second-line and Subsequent Therapy:
- AITL (**TCEL-B 3 of 5**)
- ALCL (**TCEL-B 4 of 5**)

\textsuperscript{g}Activity has been demonstrated in small clinical trials and additional larger trials are needed.
SUGGESTED TREATMENT REGIMENS FOR AITL

Second-line Therapy (with intention to proceed to transplant) and Subsequent Therapy
- Clinical trial preferred
- Preferred single agents/combination regimens
  - Single agents (alphabetical order)
    - Belinostat
    - Brentuximab vedotin for CD30+ AITL
    - Romidepsin
  - Combination regimens (alphabetical order)
    - DHAP (dexamethasone, cisplatin, cytarabine)
    - ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)
    - GDP (gemcitabine, dexamethasone, cisplatin)
    - GemOx (gemcitabine, oxaliplatin)
    - ICE (ifosfamide, carboplatin, etoposide)

Alternative Regimens
- Single agents (alphabetical order)
  - Bendamustine
  - Gemcitabine
  - Lenalidomide
  - Pralatrexate

Second-line Therapy (no intention to transplant) and Subsequent Therapy:
- Clinical trial preferred
- Preferred single agents (alphabetical order)
  - Belinostat
  - Brentuximab vedotin for CD30+ AITL
  - Romidepsin
- Alternative single agents/regimens (alphabetical order)
  - Alemtuzumab
  - Bendamustine
  - Bortezomib (category 2B)
  - Cyclosporine
  - Gemcitabine
  - Lenalidomide
  - Pralatrexate
  - Radiation therapy

See First-line Therapy on TCEL-B 1 of 5.
See Second-line and Subsequent Therapy:
- PTCL-NOS and EATL (TCEL-B 2 of 5)
- ALCL (TCEL-B 4 of 5)

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See references for regimens TCEL-B 5 of 5.

Activity has been demonstrated in small clinical trials and additional larger trials are needed.

In AITL, pralatrexate has limited activity.

With close follow-up of renal function.
SUGGESTED TREATMENT REGIMENS FOR ALCL$^a$

**Second-line Therapy (with intention to proceed to transplant) and Subsequent Therapy**
- Clinical trial preferred
- Preferred single agents/comboation regimens
  - Single agents (alphabetical order)
    - Belinostat
    - Brentuximab vedotin
    - Pralatrexate
    - Romidepsin
  - Combination regimens (alphabetical order)
    - DHAP (dexamethasone, cisplatin, cytarabine)
    - ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)
    - GDP (gemcitabine, dexamethasone, cisplatin)
    - GemOx (gemcitabine, oxaliplatin)
    - ICE (ifosfamide, carboplatin, etoposide)

**Second-line Therapy (no intention to transplant) and Subsequent Therapy**
- Clinical trial preferred
- Preferred single agents (alphabetical order)
  - Belinostat
  - Brentuximab vedotin
  - Pralatrexate
  - Romidepsin
- Alternative single agents/regimens (alphabetical order)
  - Alemtuzumab
  - Bortezomib$^g$ (category 2B)
  - Gemcitabine
  - Radiation therapy

**Alternative Regimens**
- Single agents (alphabetical order)
  - Bendamustine
  - Gemcitabine

See First-line Therapy on **TCEL-B 1 of 5**.

See Second-line and Subsequent Therapy:
- PTCL-NOS and EATL (**TCEL-B 2 of 5**)
- AITL (**TCEL-B 3 of 5**)

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$^a$See references for regimens **TCEL-B 5 of 5**.

$^g$Activity has been demonstrated in small clinical trials and additional larger trials are needed.

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

First-Line Therapy

CHOP

CHOP or CHOP-14 with or without etoposide

SCHOF followed by IV

CHOP followed by IV

Dose-adjusted EPOCH

EPOCH

HyperCVID alternating with high-dose methotrexate and cytarabine

Second-line Therapy

Alemtuzumab

Belimostat

Bendamustine

Brentuximab vedotin


GemOX (gemcitabine, oxaliplatin)

ICE (ifosfamide, carboplatin, etoposide)

Pralatrexate

Romidepsin

Cyclosporine for aITL

DHAP (dexamethasone, cisplatin, cytarabine)

ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)

Gencatibine

Belinostat

Romidepsin

Gencatibine

GDP (gencatibine, dexamethasone, cisplatin)

GEMOX (gemcitabine, oxaliplatin)

ICE (ifosfamide, carboplatin, etoposide)

ICE (ifosfamide, carboplatin, etoposide)

Pralatrexate

Romidepsin


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

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
**NCCN Guidelines Version 2.2017**
**Breast Implant-Associated ALCL**

### CLINICAL PRESENTATION

- **Physical signs**
  - Effusion, enlargement, mass, ulceration >1 year post implantation (Average 8–10 years post-implantation)

### INITIAL WORKUP

- Ultrasound of breast or Breast MRI in selected cases or PET/CT scan in selected cases
- Mass
  - Biopsy of mass
  - Ultrasound inconclusive
  - Breast MRI

### PATHOLOGIC WORKUP

- **Fine-needle aspiration (FNA) of fluid around breast implant**
- **Cytology**
  - Essential for diagnosis
  - IHC and flow cytometry for T-cell markers and CD30
- If indeterminate of lymphoma
  - Second pathology consultation by tertiary cancer center
  - Negative for lymphoma
  - Refer to plastic surgeon for management
- Histologic confirmation or suspicious of BIA-ALCL

---

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

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

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*a*Rare cases with parenchymal breast or nodal involvement may have an aggressive course more in line with systemic ALK-positive ALCL (See TCEL-3). Optimal treatment of these cases is not well defined and management should be individualized.


BIAA-2

LYMPHOMA WORKUP AND STAGING\textsuperscript{f}

- Recommend discussion by multidisciplinary team\textsuperscript{g}
- History and physical exam, including complete skin exam
- CBC, differential, comprehensive metabolic panel
- LDH
- PET/CT scan
- Echocardiogram or MUGA scan if anthracycline or anthrancenedione-based regimen is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy or RT planned)

TREATMENT

- Total capsulectomy and excision of associated mass with biopsy of suspicious node(s), explantation
- Consider removal of contralateral implant\textsuperscript{h}
- Surgical oncologist recommended\textsuperscript{i}

ADJUVANT TREATMENT

- Localized disease to capsule/implant/breast
- Incomplete excision or partial capsulectomy with residual disease
- Complete excision with no residual disease

FOLLOW-UP

- Observation\textsuperscript{j}
- Observation for every 3–6 mo for 2 y and then as clinically indicated
- ± C/A/P CT with contrast or PET/CT scan no more often than every 6 mo for 2 y then only as clinically indicated

Histologic confirmation or suspicious of BIA-ALCL\textsuperscript{e}

Extended disease (stage II–IV)

\textsuperscript{e}FDA recommends reporting all BIA-ALCL cases to the PROFILE Registry: www.thepsf.org/PROFILE.

\textsuperscript{f}For BIA-ALCL, bone marrow biopsy is only needed in selected cases.

\textsuperscript{g}Eq, oncologist, surgical oncologist, plastic surgeon, hempathologist.

\textsuperscript{h}In approximately 4.6% of cases, lymphoma was found in the contralateral breast (Clemens MW, Medeiros LJ, Butler CE, et al. Complete surgical excision is essential for the management of patients with breast implant–associated anaplastic large-cell lymphoma. J Clin Oncol 2016; 34:160-168).


NCCN Guidelines Version 2.2017
Mycosis Fungoides/Sezary Syndrome

DIAGNOSIS

ESSENTIAL:
• Biopsy of suspicious skin sites
  ▶ Multiple biopsies may be necessary to capture the pathologic variability of disease at diagnosis
• Dermatopathology review of slides\textsuperscript{a}
• IHC panel of skin biopsy\textsuperscript{b, c, d}
  ▶ CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, CD25, CD56, TIA1, granzyme B, βF1, TCR-CγM1

USEFUL UNDER CERTAIN CIRCUMSTANCES:
• Molecular analysis of skin biopsy: TCR gene rearrangements (assessment of clonality)\textsuperscript{b} by PCR methods\textsuperscript{e}
• Assessment of peripheral blood for Sezary cells (in cases where skin is not diagnostic, especially T4) including:
  ▶ Sezary cell prep
  ▶ Flow cytometry (CD3, CD4, CD7, CD8, CD26 to assess for expanded CD4+ cells with increased CD4/CD8 ratio or with abnormal immunophenotype, including loss of CD7 or CD26) and
  ▶ PCR for TCR gene rearrangement
• Biopsy of suspicious lymph nodes (in absence of definitive skin diagnosis)
• Assessment of HTLV-1\textsuperscript{f} serology in at-risk populations. HTLV-1 PCR if serology is indeterminate.

\textsuperscript{a}Presence of transformation or areas of folliculotropism may have important implications for selection of therapy and outcome and should be included in pathology reports.
\textsuperscript{c}See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (See B-cell Lymphomas Guidelines)
\textsuperscript{d}Typical immunophenotype: CD2+ CD3+ CD5+ CD7- CD4+ CD8- (rarely CD8+), CD30-/+ cytotoxic granule proteins negative.
\textsuperscript{e}TCR gene rearrangement results should be interpreted with caution. TCR clonal rearrangement can be seen in non-malignant conditions or may not be demonstrated in all cases of MF/SS. Demonstration of identical clones in skin, blood, and/or lymph node may be helpful in selected cases.
\textsuperscript{f}See map for prevalence of HTLV-1 by geographic region.

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

ESSENTIAL:
- Complete physical examination:
  - Examination of entire skin: assessment of % BSA (palm plus digits =1% BSA) and type of skin lesion (patch/plaque, tumor, erythroderma)
  - Palpation of peripheral lymph node regions
  - Palpation for organomegaly/masses
- Laboratory studies:
  - CBC with Sezary screen (manual slide review, "Sezary cell prep")
  - Sezary flow cytometric study (optional for T1\(^h\))
  - TCR gene rearrangement of peripheral blood lymphocytes if blood involvement suspected
  - Comprehensive metabolic panel
  - LDH
- Imaging studies:
  - C/A/P CT with contrast or integrated whole body (arms/legs included when disease assessment of entire body is needed) PET/CT (≥T2 or large cell transformed or folliculotropic MF, or with palpable adenopathy or abnormal laboratory studies)
- Pregnancy testing in women of child-bearing age\(^i\)

USEFUL IN SELECTED CASES:
- Bone marrow biopsy in patients with unexplained hematologic abnormality
- Biopsy (FNA is often inadequate) of suspicious lymph nodes or suspected extracutaneous sites
- Rebiopsy skin if suspicious of large-cell transformation
- Neck CT with contrast

\(^9\)Sezary syndrome (B2) is as defined on MFSS-3.
\(^h\)See Discussion for when Sezary flow cytometric study is appropriate in T1 disease.
\(^i\)Many skin-directed and systemic therapies are contraindicated or of unknown safety in pregnancy. Refer to individual drug information.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
<table>
<thead>
<tr>
<th>TNMB</th>
<th>Classification and Staging of Mycosis Fungoides and Sezary Syndrome(^{j,k})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin</strong></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Limited patches,(^{1}) papules, and/or plaques(^{m}) covering &lt;10% of the skin surface</td>
</tr>
<tr>
<td>T2</td>
<td>Patches,(^{1}) papules, and/or plaques(^{m}) covering ≥10% of the skin surface</td>
</tr>
<tr>
<td>T2a</td>
<td>Patch only</td>
</tr>
<tr>
<td>T2b</td>
<td>Plaque ± patch</td>
</tr>
<tr>
<td>T3</td>
<td>One or more tumors(^{n}) (≥1 cm in diameter)</td>
</tr>
<tr>
<td>T4</td>
<td>Confluence of erythema ≥80% body surface area</td>
</tr>
<tr>
<td><strong>Node</strong></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>No abnormal lymph nodes; biopsy not required</td>
</tr>
<tr>
<td>N1</td>
<td>Abnormal lymph nodes; histopathology Dutch Gr 1 or NCI LN 0-2</td>
</tr>
<tr>
<td>N2</td>
<td>Abnormal lymph nodes; histopathology Dutch Gr 2 or NCI LN 3</td>
</tr>
<tr>
<td>N3</td>
<td>Abnormal lymph nodes; histopathology Dutch Gr 3-4 or NCI LN 4</td>
</tr>
<tr>
<td>NX</td>
<td>Abnormal lymph nodes; no histologic confirmation</td>
</tr>
<tr>
<td><strong>Visceral</strong></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>No visceral organ involvement</td>
</tr>
<tr>
<td>M1</td>
<td>Visceral involvement (must have pathology confirmation and organ involved should be specified)</td>
</tr>
<tr>
<td>MX</td>
<td>Abnormal visceral site; no histologic confirmation</td>
</tr>
<tr>
<td><strong>Blood</strong></td>
<td></td>
</tr>
<tr>
<td>B0</td>
<td>Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes or &lt;250/mcL are atypical (Sezary) cells or &lt;15% CD4+/CD26- or CD4+/CD7- cells of total lymphocytes</td>
</tr>
<tr>
<td>B1</td>
<td>Low blood tumor burden: &gt;5% of peripheral blood lymphocytes are atypical (Sezary) cells or ≥15% CD4+CD26- or CD4+CD7- of total lymphocytes but do not meet the criteria of B0 or B2</td>
</tr>
<tr>
<td>B2</td>
<td>High blood tumor burden: ≥1000/mcL Sezary cells(^{k}) (CD4+/CD26- or CD4+/CD7- cells by flow cytometry) or CD4+/CD8 ≥10 or ≥40% CD4+/CD7- or ≥30% CD4+/CD26- cells of total lymphocytes</td>
</tr>
</tbody>
</table>


\(^{2}\)Sezary syndrome is defined by B2 blood involvement and a clonal rearrangement of the TCR in the blood (clones should be relevant to clone in the skin).

\(^{3}\)Patch = Any size skin lesion without significant elevation or induration.

\(^{4}\)Presence/absence of hypo- or hyperpigmentation, scale, crusting, and/or poikiloderma should be noted.

\(^{5}\)Plaque = Any size skin lesion that is elevated or indurated. Presence or absence of scale, crusting, and/or poikiloderma should be noted. Histologic features such as folliculotropism or large-cell transformation (≥25% large cells), CD30+ or CD30-, and clinical features such as ulceration are important to document.

\(^{6}\)Tumor = At least one ≥1 cm diameter solid or nodular lesion with evidence of depth and/or vertical growth. Note total number of lesions, total volume of lesions, largest size lesion, and region of body involved. Also note if histologic evidence of large-cell transformation has occurred. Phenotyping for CD30 is encouraged.

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**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
### Clinical Staging of MF and SS\(^j\)

<table>
<thead>
<tr>
<th></th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>B</th>
</tr>
</thead>
<tbody>
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<td>1</td>
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<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>IB</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0.1</td>
</tr>
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<td>IIA</td>
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<td>1,2</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>IIB</td>
<td>3</td>
<td>0–2</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>IIIA</td>
<td>4</td>
<td>0–2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IIIB</td>
<td>4</td>
<td>0–2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>IVA(_1)</td>
<td>1–4</td>
<td>0–2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>IVA(_2)</td>
<td>1–4</td>
<td>3</td>
<td>0</td>
<td>0–2</td>
</tr>
<tr>
<td>IVB</td>
<td>1–4</td>
<td>0–3</td>
<td>1</td>
<td>0–2</td>
</tr>
</tbody>
</table>

### NCI-VA Lymph Node Classification

- **LN0**: no atypical lymphocytes
- **LN1**: occasional and isolated atypical lymphocytes (not arranged in clusters)
- **LN2**: many atypical lymphocytes or in 3-6 cell clusters
- **LN3**: aggregates of atypical lymphocytes; nodal architecture preserved
- **LN4**: partial/complete effacement of nodal architecture by atypical lymphocytes or frankly neoplastic cells


## STAGE (MFSS-3 and MFSS-4)

### PRIMARY TREATMENT\(^{p,q}\)**

- **Stage IA\(^o\)**
  - Skin-directed therapies (may be alone or in combination with other skin-directed therapies):
    - See Suggested Treatment Regimens "Skin-Directed Therapies (Skin-Limited/Local)" (MFSS-A)
    - If B1 blood involvement
      - Consider primary treatment for Stage III, B1 MFSS-8 (category 2B)
  - CR/PR\(^r\) or inadequate response
  - Refractory disease to multiple previous therapies or progression to >stage IA on skin-directed therapies
  - Relapse with or persistent T1 skin disease
  - Systemic therapy ± skin-directed therapy (see Stage IB on page MFSS-6) or Total skin electron beam therapy (TSEBT) or Clinical trial

---

\(^o\)In rare cases of confirmed unilesional MF, RT has been shown to provide long-term remission.

\(^p\)It is preferred that treatment occur at centers with expertise in the management of the disease.

\(^q\)In patients with folliculotropism or histologic large-cell transformed MF, skin disease may be less responsive to topical therapies.

\(^r\)Unlike other NHL subtypes, response criteria for MF/SS has not been demonstrated to correlate with prognosis. Often decisions to continue or switch therapy are on a clinical basis. However, a proposal for detailed response criteria has been published (Olsen E, Whittaker S, Kim YH, et al. J Clin Oncol 2011;29:2598-2607).

\(^\)Patients with a clinical benefit and/or those with disease responding to primary treatment should be considered for maintenance or tapering of regimens to optimize response duration. Disease relapse often respond well to the same treatment. Partial response should be treated with the other options in the primary treatment options not received before to improve response before moving onto treatment for refractory disease. Patients with disease relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

---

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

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**Stage IB-IIA**

Generalized skin treatment
- See Suggested Treatment Regimens "Skin-Directed Therapies (Skin-Generalized)" (MFSS-A) ± adjuvant local skin treatment (see stage IA on MFSS-5)
- If blood B1 involvement
  - Consider primary treatment for Stage III B1 MFSS-8 (category 2B)
- If histologic evidence of folliculotropic or large-cell transformed MF
  - In selected cases, consider primary treatment for Stage IIB (See MFSS-7)

**Response to Therapy**

- CR/PR or inadequate response

**Relapse with or persistent T1-T2 disease:**
- T1 (see stage IA on MFSS-5)
- T2 (see generalized skin treatment) (MFSS-A)

**Refractory disease to multiple previous therapies or progression to > stage IB-IIA**

See Suggested Treatment Regimens
- Clinical trial
- Systemic Therapies (SYST-CAT A) (MFSS-A)
- Combination Therapies ± skin-directed therapy

**CR/PR or inadequate response**

**Refractory disease to multiple previous therapies or progression**

- Clinical trial
- TSEBT (if not previously administered)
- Systemic chemotherapy agents used in ≥ stage IIB disease

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Mycosis Fungoides/Sezary Syndrome

Stage IIB

Limited tumor lesions

Generalized tumor lesions

See Supportive Care for MF/SS (MFSS-A)

Primary Treatment

Skin-directed therapies ± local RT or Systemic Therapies (SYST-CAT A) (MFSS-A) ± local RT

Response to Therapy

CR/PR or inadequate response

Relapse with or persistent T1-T3 limited:
- T1-2 (see stage IA on MFSS-5 or stage IB-IIA on MFSS-6)
- T3 limited extent

Refactory disease to multiple previous therapies or progression

Stage II B

- TSEBT
- See Suggested Treatment Regimens ± skin-directed therapy
  - Systemic Therapies (SYST-CAT A) (MFSS-A)
  - Systemic Therapies (SYST-CAT B) (MFSS-A)
  - Systemic Therapies (SYST-CAT C) (MFSS-A)
  - Combination Therapies

CR/PR or inadequate response

Relapse with or persistent T1-T3:
- T1-2 (see stage IA on MFSS-5 or stage IB-IIA on MFSS-6)
- T3

Refactory disease to multiple previous therapies or progression

- Multi-agent chemotherapy
- Consider allogeneic transplant
- Clinical trial

Histologic evidence of LCT often, but not always corresponds to a more aggressive growth rate. If there is no evidence of more aggressive growth, choosing systemic therapies from SYST-CAT A or SYST-CAT B are appropriate. If aggressive growth is seen, then agents listed in SYST-CAT C are preferred.

Patients with indolent/plaque folliculotropic MF (without evidence of LCT) should first be considered for therapies under SYST-CAT A before resorting to treatments listed in SYST-CAT B or SYST-CAT C.

RT is preferred for tumor lesions.

May consider adjuvant systemic biologic therapy (SYST-CAT A) after TSEBT to improve response duration.

Most patients are treated with multiple SYST-CAT A/B or combination therapies before receiving multiagent chemotherapy.

The role of allogeneic HSCT is controversial. See Discussion for further details.

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

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
STAGE
(MFSS-2 and MFSS-3)

If no blood involvement, consider skin-directed therapy
See Suggested Treatment Regimens Skin-Directed Therapies (Skin-Generalized)ee (MFSS-A)
or
If blood B1 involvement, systemic therapies
See Suggested Treatment Regimens "Systemic Therapies (SYST-CAT A)" ± skin-directed therapyff

Stage III

CR/PRs or inadequate response
Relapse or persistent disease

CR/PRs or inadequate response
Relapse or persistent disease

Combination therapies
See Suggested Treatment Regimens - Combination Therapiesgg (MFSS-A)
Clinical trial

Combination therapies
See Suggested Treatment Regimens - Combination Therapiesgg (MFSS-A)
Clinical trial

Refractory disease to multiple previous therapies or progression

Refractory disease to multiple previous therapies or progression

Systemic Therapies (SYST-CAT B)
Alemtuzumabhh
Consider nonmyeloablative allogeneic transplant,dd as appropriate

TSEBT may not be well-tolerated in stage III and should be used with caution. In selected cases, TSEBT may be used with lower doses and slower fractionation.
Mid-potency topical steroids should be included (± occlusive modality) with any of the primary treatment modalities to reduce skin symptoms. Erythrodermic patients are at increased risk for secondary infection with skin pathogens and systemic antibiotic therapy should be considered.
Combination therapy options can be considered earlier (primary treatment) depending on treatment availability or symptom severity.
Lower doses of alemtuzumab administered subcutaneously have shown lower incidence of infectious complications.

The role of allogeneic HSCT is controversial. See Discussion for further details.

PIt is preferred that treatment occur at centers with expertise in the management of the disease.

Unlike other NHL subtypes, response criteria for MF/SS has not been demonstrated to correlate with prognosis. Often decisions to continue or switch therapy are on a clinical basis. However, a proposal for detailed response criteria has been published (Olsen E, Whittaker S, Kim YH, et al. J Clin Oncol 2011;29:2598-2607).

Patients with a clinical benefit and/or those with disease responding to primary treatment should be considered for maintenance or tapering of regimens to optimize response duration. Disease relapse often respond well to the same treatment. Partial response should be treated with the other options in the primary treatment options not received before to improve response before moving onto treatment for refractory disease. Patients with disease relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

Imaging indicated when suspicious of clinical extracutaneous disease with modalities used in workup.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
# NCCN Guidelines Version 2.2017

## Mycosis Fungoides/Sezary Syndrome

### STAGE

*(MFSS-2 and MFSS-3)*

<table>
<thead>
<tr>
<th>Stage IV</th>
<th>Non Sezary or Visceral disease (solid organ)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>See Suggested Treatment Regimens</td>
</tr>
<tr>
<td></td>
<td>• Systemic Therapies <em>(SYST-CAT A)</em> <em>(MFSS-A)</em></td>
</tr>
<tr>
<td></td>
<td>• Combination Therapies</td>
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### PRIMARY TREATMENT

<table>
<thead>
<tr>
<th>Sezary syndrome</th>
<th>See Suggested Treatment Regimens</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>• Systemic Therapies <em>(SYST-CAT A)</em></td>
</tr>
<tr>
<td></td>
<td>• Combination Therapies</td>
</tr>
</tbody>
</table>

### RESPONSE TO THERAPY

<table>
<thead>
<tr>
<th>CR/PR() or inadequate response</th>
<th>Relapse or persistent disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Consider allogeneic transplant,(dd) as appropriate</td>
</tr>
<tr>
<td></td>
<td>• Alemtuzumab(hh)</td>
</tr>
<tr>
<td></td>
<td>• Clinical trial</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Refractory disease to multiple previous therapies or progression</th>
<th>Clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>• See Suggested Treatment Regimens - Systemic Therapies <em>(SYST-CAT B)</em> <em>(MFSS-A)</em></td>
<td></td>
</tr>
<tr>
<td>• Alemtuzumab(hh)</td>
<td></td>
</tr>
<tr>
<td>• Clinical trial</td>
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</tbody>
</table>

### CR/PR\(\) or inadequate response

<table>
<thead>
<tr>
<th>Repeat imaging with modalities used in workup (frequency as clinically indicated)</th>
<th>Relapse or persistent disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Consider allogeneic transplant,(dd) as appropriate</td>
<td></td>
</tr>
<tr>
<td>• Alemtuzumab(hh)</td>
<td></td>
</tr>
<tr>
<td>• Clinical trial</td>
<td></td>
</tr>
</tbody>
</table>

### See Suggested Treatment Regimens - Systemic Therapies *(SYST-CAT B)* *(MFSS-A)*

### See Supportive Care for MF/SS *(MFSS-B)*

### See monoclonal antibody and viral reactivation *(LYMPH-A)*

---

\(P\)It is preferred that treatment occur at centers with expertise in the management of the disease.

\(S\)Unlike other NHL subtypes, response criteria for MF/SS has not been demonstrated to correlate with prognosis. Often decisions to continue or switch therapy are on a clinical basis. However, a proposal for detailed response criteria has been published (Olsen E, Whittaker S, Kim YH, et al. J Clin Oncol 2011;29:2598-2607).

\(R\)Patients with a clinical benefit and/or those with disease responding to primary treatment should be considered for maintenance or tapering of regimens to optimize response duration. Disease relapse often respond well to the same treatment. Partial response should be treated with the other options in the primary treatment options not received before to improve response before moving onto treatment for refractory disease. Patients with disease relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

\(D\)The role of allogeneic HSCT is controversial. See Discussion for further details.

\(H\)Lower doses of alemtuzumab administered subcutaneously have shown lower incidence of infectious complications.

\(I\)Patients with stage IV non-Sezary/visceral disease may present with more aggressive growth characteristics. If there is no evidence of more aggressive growth, systemic therapies from SYST-CAT B are appropriate. If aggressive growth is seen, then agents listed in SYST-CAT C are preferred.

\(J\)Consider adjuvant systemic biologic therapy *(SYST-CAT A)* after chemotherapy to improve response duration.

\(K\)If disease in lymph nodes and/or viscera or suspicious of disease progression, imaging indicated with modalities used in workup as clinically indicated based on distribution of disease.

---

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SKIN-DIRECTED THERAPIES

For limited/localized skin involvement (Skin-Limited/Local)
• Topical corticosteroids
• Topical chemotherapy (methotrexate [nitrogen mustard])
• Local radiation (8–36 Gy)
• Topical retinoids (bexarotene, tazarotene)
• Phototherapy (UVB, NB-UVB for patch/thin plaques; PUVA for thicker plaques)
• Topical imiquimod

For generalized skin involvement (Skin-Generalized)
• Topical corticosteroids
• Topical chemotherapy (methotrexate [nitrogen mustard])
• Phototherapy (UVB, NB-UVB, for patch/thin plaques; PUVA for thicker plaques)
• Total skin electron beam therapy (TSEBT) (12–36 Gy)

SUGGESTED TREATMENT REGIMENS

SYSTEMIC THERAPIES

Category A (SYST-CAT A)
• Retinoids (bexarotene, all-trans retinoic acid, isotretinoin [13-cis-retinoic acid], acitretin)
• Interferons (IFN-alpha, IFN-gamma)
• HDAC-inhibitors (vorinostat, romidepsin)
• Extracorporeal photopheresis
• Methotrexate (≤100 mg q week)

Category B (SYST-CAT B)
• First-line therapies (alphabetical order)
  ‣ Brentuximab vedotin
  ‣ Gemcitabine
  ‣ Liposomal doxorubicin
  ‣ Low-dose pralatrexate
• Second-line therapies
  ‣ Chlorambucil
  ‣ Pentostatin
  ‣ Etoposide
  ‣ Cyclophosphamide
  ‣ Temozolomide
  ‣ Methotrexate (>100 mg q week)
  ‣ Pembrolizumab (category 2B)
  ‣ Bortezomib (category 3)

SYSTEMIC THERAPIES (continued)

Category C (SYST-CAT C) (alphabetical order)
• Bortezomib (category 3)
• Brentuximab vedotin
• Gemcitabine
• Liposomal doxorubicin
• Low- or standard-dose pralatrexate
• Romidepsin
• See regimens listed on TCEL-B 2 of 5 (PTCL-NOS)

COMBINATION THERAPIES

Skin-directed + Systemic
• Phototherapy + retinoid
• Phototherapy + IFN
• Phototherapy + photopheresis
• Total skin electron beam + photopheresis

Systemic + Systemic
• Retinoid + IFN
• Photopheresis + retinoid
• Photopheresis + IFN
• Photopheresis + retinoid + IFN

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

**References**

**Total skin electron beam therapy (TSEBT)**


**Systemic Therapies**

**Alemtuzumab for Sezary syndrome ± lymph node disease**


**Bortezomib**


**Brentuximab vedotin**


**Retinoids**


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**SUGGESTED TREATMENT REGIMENS**

### References

**Gemcitabine**


**Pentostatin**


**Temozolomide**


**Pralatrexate**


**Pembrolizumab**

SUGGESTED TREATMENT REGIMENS

Combination Therapies

Skin-directed + Systemic


Systemic + Systemic


Allogeneic stem cell transplant


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SUPPORTIVE CARE FOR MF/SS

Collaboration with dermatologist for supportive care is essential.

**Pruritus**

- Assessment
  - Pruritus should be assessed at each visit using consistent measurements
  - Generalized pruritus and localized pruritus should be distinguished
  - Correlation between sites of disease and localization of pruritus should be noted
  - Other potential causes for pruritus should be ruled out

- Treatment
  - Moisturizers and emollients
  - Topical steroid (appropriate strength for body region) ± occlusion
  - Optimize skin-directed and systemic therapy
  - Topical preparations - camphor/menthol formulations, pramoxine formulations
  - Systemic agents
    - **First-line**
      - Antihistamines
      - Doxepin
      - Gabapentin
    - **Second-line**
      - Aprepitant
      - Mirtazapine
      - Selective serotonin reuptake inhibitors
  - **Third-line**
    - Naltrexone

**Infections**

- **Active or Suspected Infections**
  - Cutaneous viral infections
    - High risk for skin dissemination of localized viral infections (HSV/VZV)
  - Erythroderma:
    - Skin swab and nares cultures for Staphylococcus aureus (S. aureus) infection or colonization
    - Intranasal mupirocin
    - Oral dicloxacillin or cephalaxin
    - Sulfamethoxazole/trimethoprim, doxycycline if suspect MRSA
    - Vancomycin if no improvement or bacteremia
    - Bleach baths or soaks (if limited area)
  - Ulcerated and necrotic tumors:
    - Gram-negative rods (GNR) common in necrotic tumors may lead to bacteremia and sepsis
    - If high suspicion for infection, obtain blood cultures, start antibiotics even if fever absent
    - Role of wound cultures not clear due to colonization
    - Empirical therapy for both GNR and gram-positive coccal infections is necessary initially

- **Prophylaxis**
  - Optimize skin barrier protection
  - Mupirocin for S. aureus colonization
  - Diluted bleach baths or soaks (if limited area)
    - Either 2 teaspoons of bleach in 1 gallon of water OR 1 quarter of a cup (NOT 1 cup) of bleach in a bathtub of water
  - Avoid central lines (especially in erythrodermic patients)
  - For patients receiving alemtuzumab, see LYMP-A.

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OVERVIEW & DEFINITION

• Primary cutaneous CD30+ T-cell lymphoproliferative disorders (LPDs) represent a spectrum that includes primary cutaneous anaplastic large cell lymphoma (ALCL), lymphomatoid papulosis, and “borderline” cases with overlapping clinical and histopathologic features.a,b

• Clinical correlation with histopathologic features is essential for establishing the diagnosis of primary cutaneous CD30+ T-cell LPDs; diagnosis cannot be made based on pathology review alone.

Differential diagnosis

• It is critical to distinguish CD30+ T-cell LPDs from other CD30+ processes involving the skin that include:
  › Systemic lymphomas (eg, systemic ALCL, ATLL, PTCL),
  › Other cutaneous process such as other CD30+ skin lymphomas such as mycosis fungoides (MF), especially transformed MF, cytotoxic T-cell lymphomas, and
  › Benign disorders such as lymphomatoid drug reactions, arthropod bites, viral infections, and others.

• Lymphomatoid drug reactions have been linked with certain drugs (eg, amlodipine, carbamazepine, cefuroxime, valsartan) and are associated with CD30+ atypical large cells in histology

• MF and primary cutaneous CD30+ T-cell LPD can coexist in the same patient.

• Primary cutaneous ALCL (PC-ALCL)
  › Represents about 8% of cutaneous lymphoma cases.b
  › Unlike systemic ALCL, PC-ALCL typically follows an indolent course and although cutaneous relapses are common an excellent prognosis is usually maintained.c
  › Histologically characterized by diffuse, cohesive sheets of large CD30-positive (in >75%) cells with anaplastic, pleomorphic, or immunoblastic appearance.a,b
  › Clinical features typically include solitary or localized nodules or tumors (often ulcerated); multifocal lesions occur in about 20% of cases. Extracutaneous disease occurs in about 10% of cases, usually involving regional lymph nodes.a,b Patches and plaques may also be present and some degree of spontaneous remittance in lesions may also be seen.

• Lymphomatoid papulosis (LyP)
  › LyP has been classified (WHO-EORTC) under lymphomas but may be best classified as a LPD as it is a uniformly spontaneously regressing process.b
  › LyP has been reported to be associated with other lymphomas such as MF, PC-ALCL, systemic ALCL, or Hodgkin lymphoma.d,e
  › Histologically heterogenous with large atypical anaplastic, immunoblastic, or Hodgkin-like cells in a marked inflammatory background;a several histologic subtypes (types A to D and other types, with CD30-positive cells) defined based on evolution of skin lesions.d
  › Clinical features characterized by chronic, recurrent spontaneously regressing papulonodular (grouped or generalized) skin lesions.a,b,d

See Diagnosis (PCTLD-2)

eDue to overlapping immunophenotype and morphology, need to use caution to not diagnose CD30+ T-cell in lymph nodes as HL (Eberle FC, Song JY, Xi L, et al. Nodal involvement by cutaneous CD30-positive T-cell lymphoma mimicking classical Hodgkin lymphoma. Amer J Surg Pathol 2012;36:716-725.)
## DIAGNOSIS

### ESSENTIAL:
- Clinical presentation: see Overview and Definition
- Clinical pathologic correlation is essential
- Complete skin examination for evidence of MF
- Biopsy of suspicious skin sites
  - Histopathology review of adequate biopsy (punch, incisional, or excisional).
  - Review of all slides with at least one paraffin block representative of the tumor should be done by a pathologist with expertise in the diagnosis of cutaneous T-cell lymphoma.
  - Rebiopsy if consult material is nondiagnostic.
- Biopsy of all types of clinical lesions present will aid in final diagnosis.
- Adequate immunophenotyping to establish diagnosis on skin biopsy:
  - IHC: CD3, CD4, CD8, CD20, CD30, CD56, βF1, ALK

### USEFUL UNDER CERTAIN CIRCUMSTANCES:
- On skin biopsy:
  - Expanded IHC: CD2, CD5, CD7, CD25, TIA1, granzyme B, perforin, GM1, EBER-ISH, MUM1, FISH 6p25.3, EMA
  - Molecular analysis to detect gene rearrangements: TCR (assessment of clonality)
  - Excisional or incisional biopsy of suspicious lymph nodes
  - Assessment of HTLV-1 serology in at-risk populations to identify CD30+ ATLL

### CD30+ transformed mycosis fungoides
- See Mycosis Fungoides Guidelines (MFSS-1)

### Cutaneous ALCL
- See Workup (PCTLD-3)

### LyP
- See Mycosis Fungoides Guidelines (MFSS-1)

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Due to overlapping immunophenotype and morphology, need to use caution to not diagnose CD30+ T-cell in lymph nodes as HL (Eberle FC, Song JY, Xi L, et al. Nodal involvement by cutaneous CD30-positive T-cell lymphoma mimicking classical Hodgkin lymphoma. Amer J Surg Pathol 2012;36:716-725.)

LyP is not considered a malignant disorder; however, there is an association with other lymphoid malignancy (mycosis fungoides or PC-ALCL). Staging studies are done in LyP only if there is suspicion of systemic involvement by an associated lymphoma.

Monitoring the size and number of lesions will assist with response assessment.

Consider systemic ALC, regional lymph node involvement with PC-ALCL, or lymph node involvement with transformed MF.

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

Only done to exclude an associated lymphoma.

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
### Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders

#### Cutaneous ALCL with regional node (excludes systemic ALCL)

<table>
<thead>
<tr>
<th>SUBTYPE</th>
<th>EXTENT OF DISEASE</th>
<th>PRIMARY TREATMENT</th>
<th>FOLLOW-UPS</th>
<th>RELAPSED/REFRACTORY DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Solitary or grouped lesions</td>
<td>Surgical excision ± RT(^{q}) or RT(^{q})</td>
<td>Response</td>
<td>Retreat with initial treatment if disease confined to skin</td>
</tr>
<tr>
<td>Multifocal lesions</td>
<td>Methotrexate (≤100 mg weekly) or RT(^{q}) or Systemic retinoids(^{r}) or Pralatrexate or Brentuximab vedotin or Observation, if asymptomatic or Interferon (category 3)</td>
<td>Observe for recurrence</td>
<td>No response/refractory</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methotrexate ± RT(^{q}) or Pralatrexate ± RT(^{q}) or Brentuximab vedotin ± RT(^{q}) or CHOP or CHOEP ± RT(^{q}) in selected cases or RT(^{q}) in selected cases</td>
<td>Response(^{t})</td>
<td>Observe for recurrence</td>
<td></td>
</tr>
</tbody>
</table>

\(^{p}\)Regression of lesions may occur in up to 44% of cases.

\(^{q}\)See *Principles of Radiation Therapy (LYMP-C)*.

\(^{r}\)Limited data from case reports (eg, bexarotene).

\(^{t}\)Mycosis fungoides can develop over time; continue to conduct thorough skin exam during follow-up.

\(^{t}\)Patients with cutaneous disease achieving a clinical benefit and/or those with disease responding to primary treatment should be considered for maintenance or tapering of regimens to optimize response duration. Disease relapse often respond well to the same treatment. Partial response should be treated with the other options in the primary treatment options not received before to improve response before moving onto treatment for refractory disease. Patients with disease relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

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**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
**Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders**

**SUBTYPE**

**EXTENT OF DISEASE**

**PRIMARY TREATMENT**

<table>
<thead>
<tr>
<th>Limited lesions or asymptomatic</th>
<th>Observation (preferred for asymptomatic) or Topical steroids or Phototherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive lesions or symptomatic</td>
<td>Observation or Methotrexate [10–35 mg weekly] or Phototherapy or Systemic retinoids or Topical steroids or Topical mechlorethamine (nitrogen mustard)</td>
</tr>
</tbody>
</table>

**FOLLOW-UP**

<table>
<thead>
<tr>
<th>Asymptomatic disease</th>
<th>Observe for recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic disease</td>
<td></td>
</tr>
</tbody>
</table>

**RELAPSED/REFRACTORY DISEASE**

<table>
<thead>
<tr>
<th>Continue observation or Topical steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat with alternative regimen not used for primary treatment or Other regimens</td>
</tr>
<tr>
<td>Clinical trial or Observation or Retreat or treat with alternative regimen not used for primary treatment</td>
</tr>
<tr>
<td>If refractory</td>
</tr>
</tbody>
</table>

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\(^{1}\)Limited data from case reports (eg, bexarotene).


\(^{3}\)Life-long follow-up is warranted due to high risks for second lymphoid malignancies; continue to conduct thorough skin exam during follow-up.

\(^{4}\)Patients with a clinical benefit and/or those with disease responding to primary treatment should be considered for maintenance or tapering of regimens to optimize response duration. Disease relapse often respond well to the same treatment. Partial response should be treated with the other options in the primary treatment options not received before to improve response before moving onto treatment for refractory disease. Patients with disease relapse or persistent disease after initial primary treatment may be candidates for clinical trials.
**REFERENCES**

**Systemic therapies (Continued)**

**Pralatrexate**


**Systemic retinoids**


**Interferons**


**Brentuximab vedotin**


**Skin-directed therapies**

**Topical steroids**


**Phototherapy**


**Topical nitrogen mustard**


**Radiation therapy**


**Systemic therapies**

**Methotrexate**


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

**ESSENTIAL:**
- Peripheral blood smear analysis for cytology; presence of larger lymphocytes characterized by reniform or round nucleus and abundant cytoplasm containing azurophilic granules
- Flow cytometry on peripheral blood
- Bone marrow aspirate and biopsy
- Adequate immunophenotyping to establish diagnosis
  - Cell surface marker analysis by flow cytometry: CD3, CD4, CD5, CD7, CD8, CD16, CD56, CD57, CD28, TCRαβ, TCRγδ, CD45RA, CD62L with or without
  - IHC panel: CD3, CD4, CD5, CD7, CD8, CD56, CD57, TCRαβ, TCRγ, TIA1, perforin, granzyme B

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Flow cytometry to assess clonality: TCR Vβ
- Mutational analysis: STAT3 and STAT5B
- Molecular analysis to detect gene rearrangement
  - TCRαβ, TCRγ
- IHC panel: granzyme M
- EBER-ISH

---

**WORKUP**

**ESSENTIAL:**
- History and physical examination: evaluation of enlarged spleen, liver; presence of lymphadenopathy (rare)
- Presence of autoimmune disease (especially rheumatoid arthritis [RA])
- Performance status
- CBC, differential, platelets
- Comprehensive metabolic panel
- Serologic studies: HIV-1,2, HTLV-1,2
- PCR for viral DNA or RNA: HBV, HCV, EBV, CMV
- Pregnancy testing in women of child-bearing age (if chemotherapy or RT planned)

**USEFUL IN SELECTED CASES:**
- Serological markers (eg, RF, ANA, ESR) for autoimmune disease
- Ultrasound of liver/spleen
- C/A/P CT with contrast of diagnostic quality
- Echocardiography

---

[a] Autoimmune disorders such as rheumatoid arthritis can occur in patients with T-cell large granular lymphocytic (LGL) leukemia. Small, clinically non-significant clones of T-cell LGLs can be detected concurrently in patients with bone marrow failure disorders.

[b] Rule out reactive LGL lymphocytosis. Repeat peripheral blood flow cytometry and TCR gene rearrangement studies in 6 months in asymptomatic patients with small clonal LGL populations (<0.5 × 10^9/L) or polyclonal LGL lymphocytosis.

[c] Typically needed to confirm diagnosis; essential for cases with low T-LGL counts (<0.5 × 10^9/L) and cases suspicious for concurrent bone marrow failure disorders.

[d] Typical immunophenotype for T-LGL: CD3+ CD8+ CD16+ CD57+ CD56- CD28- CD5 dim and/or CD7 dim CD45RA+ CD62L- TCRαβ+ TIA1+ granzyme B+ granzyme M+.

[e] TCR gene rearrangement results should be interpreted with caution. Clonal TCR gene rearrangement without cytologic and immunophenotypic evidence of abnormal T-cell population does not constitute a diagnosis of T-cell malignancy since it can be seen in healthy subjects.

[f] In patients with unexplained shortness of breath and/or right heart failure.

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Methotrexate with or without steroids may be beneficial in patients with autoimmune disease; cyclophosphamide or cyclosporine may be used as a first- or second-line option in patients with anemia.

Complete response is defined as: recovery of blood counts to Hgb >12 g/dL, ANC >1.5 x 10^9/L, platelet >150 x 10^9/L, resolution of lymphocytosis (<4 x 10^9/L) and circulating LGL counts within normal range (<0.5 x 10^9/L). Partial response is defined as: recovery of hematologic parameters to Hgb >8 g/dL, ANC >0.5 x 10^9/L, platelet >50 x 10^9/L, and absence of transfusions.

Limit therapy with cyclophosphamide to 4 mo if no response and to ≤12 mo if PR observed at 4 mo due to increased risk of leukemogenesis. Other options include purine analogues and alemtuzumab.

While alemtuzumab is no longer commercially available, it may be obtained for clinical use.
**Adult T-Cell Leukemia/Lymphoma**

**ESSENTIAL:**
- CBC and peripheral blood smear for atypical cells:
  - Lymphocytosis (ALC >4000/µL in adults) in acute and chronic subtypes
- Flow cytometry on peripheral blood
- HTLV-1 serology:
  - ELISA and confirmatory western blot if ELISA is positive. If western blot is indeterminate, then HTLV-1 PCR can be performed

**USEFUL IN CERTAIN CIRCUMSTANCES:**
- Biopsy of lymph nodes (excisional), skin biopsy, GI tract, or bone marrow biopsy is required if:
  - Diagnosis is not established on peripheral blood, or
  - Ruling out an underlying infection (eg, tuberculosis, histoplasmosis, toxoplasmosis)
- If biopsy performed, the recommended panel for paraffin section immunohistochemistry:
  - CD3, CD4, CD5, CD7, CD8, CD25, CD30

**ESSENTIAL:**
- Complete H&P examination, including complete skin exam
- Electrolytes, BUN, creatinine, serum calcium, serum LDH
- Chest/abdominal/pelvic/neck CT with contrast
- Pregnancy testing in women of child-bearing age
  - (if chemotherapy or RT planned)

**USEFUL IN SELECTED CASES:**
- Upper gastrointestinal endoscopy
- Skeletal survey in symptomatic patients
- Stool examination for parasites (strongyloides is most likely)
- PET/CT scan
- Central nervous system evaluation: Head CT or MRI with contrast and/or lumbar puncture in all patients with acute or lymphoma subtypes or in patients with neurologic manifestations

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*aThe diagnosis of ATLL requires histopathology and immunophenotyping of tumor lesion, or morphology and immunophenotyping of peripheral blood, and HTLV-1 serology.

*bSee map for prevalence of HTLV-1 by geographic region.

*cTypical ATL cells (“flower cells”) have distinctly polylobated nuclei with homogeneous and condensed chromatin, small or absent nucleoli, and agranular and basophilic cytoplasm, but multiple morphologic variations can be encountered. Presence of ≥5% atypical cells by morphology in peripheral blood is required for diagnosis in the absence of other criteria.


*eTypical immunophenotype: CD2+ CD3+ CD4+ CD5+ CD7- CD8- CD25+ CD30-/+ TCRαβ+. Presence of ≥5% T-lymphocytes with an abnormal immunophenotype in peripheral blood is required for diagnosis.

*fBone marrow involvement is an independent poor prognostic factor.

*gSee Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (See B-cell Lymphomas Guidelines).

*hUsually CD4+ T-cells with expression of CD2, CD5, CD25, CD45RO, CD29, T-cell receptor αβ, and HLA-DR. Most cases are CD7- and CD26- with low CD3 expression. Rare cases are CD8+ or CD4/CD8 double positive or double negative.

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### ATLL SUBTYPE

<table>
<thead>
<tr>
<th>Chronic/Smoldering</th>
<th>FIRST-LINE THERAPY</th>
<th>INITIAL RESPONSE</th>
<th>Consider prophylaxis for tumor lysis syndrome (<a href="#">See LYMPH-A</a>)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trial or Observation or Skin-directed therapies as clinically indicated (<a href="#">See Mycosis Fungoides/Sezary Syndrome [MFSS-A]</a>) or Zidovudine and interferon</td>
<td>Responses</td>
<td>Continue treatment with zidovudine and interferon</td>
<td></td>
</tr>
<tr>
<td>Non-responders</td>
<td></td>
<td>Clinical trial or Chemotherapy (<a href="#">See Suggested Initial Chemotherapy Regimens [ATLL-B]</a>) or Best supportive care</td>
<td></td>
</tr>
</tbody>
</table>

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**ATLL-A:**
- Supportive care: anti-infectious prophylaxis with sulfamethoxazole/trimethoprim + strongyloidosis is recommended.
- Outside of a clinical trial, if the disease is not responding or is progressing, treatment with zidovudine and interferon should be stopped. If there is evidence of clinical benefit, treatment should continue until best response is achieved. If life-threatening manifestations, treatment can be discontinued before the 2-month period.
- See references for zidovudine and interferon ([ATLL-C](#)).
- If nodal disease is present, repeat C/A/P CT with contrast or PET/CT.
- See [Response Criteria for ATLL (ATLL-A)](#). Responders include CR, uncertified PR, and PR.
# ATLL Subtype

<table>
<thead>
<tr>
<th>ATLL Subtype</th>
<th>First-Line Therapy</th>
<th>Initial Response</th>
<th>Response Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>Clinical trial or Zidovudine and interferon or Chemotherapy ([See Suggested Initial Chemotherapy Regimens [ATLL-B])]</td>
<td>Responders (after 2 cycles)</td>
<td>Continue prior therapy or Consider allogeneic stem cell transplant</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Clinical trial or Chemotherapy ([See Suggested Initial Chemotherapy Regimens [ATLL-B]])</td>
<td>Responders</td>
<td>Continue chemotherapy or Consider allogeneic stem cell transplant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-responders</td>
<td></td>
</tr>
</tbody>
</table>

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RESPONSE CRITERIA FOR ATLL

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
<th>Lymph Nodes</th>
<th>Extranodal Masses</th>
<th>Spleen, Liver</th>
<th>Skin</th>
<th>Peripheral Blood</th>
<th>Bone Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission*</td>
<td>Disappearance of all disease</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal†</td>
<td>Normal</td>
</tr>
<tr>
<td>Uncertified complete remission*</td>
<td>Stable residual mass in bulky lesion</td>
<td>≥75% decrease†</td>
<td>≥75% decrease†</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal†</td>
<td>Normal</td>
</tr>
<tr>
<td>Partial remission*</td>
<td>Regression of disease</td>
<td>≥50% decrease†</td>
<td>≥50% decrease†</td>
<td>No increase</td>
<td>≥50% decrease</td>
<td>≥50% decrease</td>
<td>Irrelevant</td>
</tr>
<tr>
<td>Stable disease*</td>
<td>Failure to attain complete/partial remission and no progressive disease</td>
<td>No change in size</td>
<td>No change in size</td>
<td>No change in size</td>
<td>No change in size</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Relapsed disease or progressive disease</td>
<td>New or increased lesions</td>
<td>New or ≥50% increase§</td>
<td>New or ≥50% increase§</td>
<td>New or ≥50% increase</td>
<td>≥50% increase</td>
<td>New or ≥50% increase#</td>
<td>Reappearance</td>
</tr>
</tbody>
</table>

*Required that each criterion be present for a period of at least 4 weeks.
†Provided that <5% of flower cells remain, complete remission is judged to have been attained if the absolute lymphocyte count, including flower cells, is <4 x 10^9/L.
‡Calculated by the sum of the products of the greatest diameters of measurable disease.
§Defined by ≥50% increase from nadir in the sum of the products of measurable disease.
#Defined by ≥50% increase from nadir in the count of flower cells and an absolute lymphocyte count, including flower cells, of >4 x 10^9/L.

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NCCN Guidelines Version 2.2017
Adult T-Cell Leukemia/Lymphoma

SUGGESTED TREATMENT REGIMENS
(in alphabetical order)

• Initial Chemotherapy
  ‣ CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)
  ‣ CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone)
  ‣ Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin)
  ‣ HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine

• Second-line Therapy (with intention to proceed to HDT/ASCR) or Subsequent Therapy to HDT/ASCR
  • Clinical trial preferred
  • Preferred single agents/combination regimens
    ‣ Single agents (alphabetical order)
      ◊ Brentuximab vedotin for CD30 expressing cases
      ◊ Lenalidomide
    ‣ Combination regimens (alphabetical order)
      ◊ Interferon and zidovudine (smoldering and chronic subtypes)
      ◊ DHAP (dexamethasone, cisplatin, cytarabine)
      ◊ ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)
      ◊ GDP (gemcitabine, dexamethasone, cisplatin)
      ◊ GemOx (gemcitabine, oxaliplatin)
      ◊ ICE (ifosfamide, carboplatin, etoposide)
      ◊ GVD (gemcitabine, vinorelbine, liposomal doxorubicin)

Alternative Regimens
• Single agents (alphabetical order)
  ‣ Alemtuzumab
  ‣ Arsenic trioxide/interferon alpha
  ‣ Belinostat
  ‣ Bendamustine
  ‣ Bortezomib
  ‣ Gemcitabine
  ‣ Pralatrexate
  ‣ Radiation therapy in selected cases with localized, symptomatic disease

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

Zidovudine and interferon


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T-Cell Prolymphocytic Leukemia

**DIAGNOSIS**

**ESSENTIAL:**
- Tissue histology not essential for diagnosis
- Peripheral blood smear analysis for morphology
- Peripheral blood flow cytometry to establish diagnosis
  - TdT, CD1a, CD2, CD3, CD4, CD5, CD7, CD8, CD52, TCRαβ
- Cytogenetics: inv(14)(q11;q32); t(14;14)(q11;q32); t(X;14)(q28;q11); trisomy 8

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Molecular analysis to detect: TCRβ, TCRγ gene rearrangement; MTCP1 gene rearrangement; ATM mutation;
- IHC: TCL1 overexpression
- Bone marrow biopsy
  - IHC panel: CD1a, TdT, CD2, CD3, CD5, TCL1

**WORKUP**

**ESSENTIAL:**
- Complete H&P examination, including complete skin exam, and evaluation of lymph nodes, spleen, and liver.
- Performance status
- LDH, electrolytes, BUN, creatinine
- CBC, differential
- Chest/abdomen/pelvis CT with contrast
- Pregnancy testing in women of child-bearing age (if chemotherapy or RT planned)

**USEFUL IN SELECTED CASES:**
- Echocardiogram or MUGA scan if treatment includes regimens containing anthracyclines or anthracenediones
- Bone marrow evaluation
- PET/CT scan
- HTLV-1 serology: ELISA and confirmatory Western blot if ELISA positive
- Consider screening for active infections and CMV serology if therapy with alemtuzumab is contemplated

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### T-Cell Prolymphocytic Leukemia

<table>
<thead>
<tr>
<th>SYMPTOMATIC DISEASE</th>
<th>PRIMARY TREATMENT</th>
<th>INITIAL RESPONSE</th>
<th>CONSOLIDATION C</th>
<th>SECOND-LINE THERAPY C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic disease</td>
<td>• Clinical trial (preferred)</td>
<td>Complete or partial response</td>
<td>Consider allogeneic stem cell transplant (if donor available)</td>
<td>• Clinical trial (preferred)</td>
</tr>
<tr>
<td></td>
<td>• Intravenous alemtuzumab alone</td>
<td></td>
<td></td>
<td>• Consider alternate regimens not used in primary treatment</td>
</tr>
<tr>
<td></td>
<td>• Alemtuzumab-containing regimens</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>‣ FMC (fludarabine, mitoxantrone, cyclophosphamide) followed by IV alemtuzumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>‣ IV alemtuzumab and pentostatin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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---

**Consider prophylaxis for tumor lysis syndrome ([See LYMPH-A](#))**

**See monoclonal antibody and viral reactivation ([LYMPH-A](#))**

---

**References:**


2. **Monitor for CMV reactivation; anti-infective prophylaxis for herpes virus and PCP is recommended when treating with alemtuzumab ± purine analogs.**
TREATMENT REFERENCES

**Alemtuzumab**

**Alemtuzumab + pentostatin**

**FMC (fludarabine, mitoxantrone, cyclophosphamide) followed by alemtuzumab**

**Allogeneic stem cell transplant**
**Extranodal NK/T-Cell Lymphoma, nasal type**

### 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 suitable for the initial diagnosis of lymphoma.\(^b\)
- In certain circumstances, when tissue is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for antigen receptor rearrangements, and FISH for major translocations) may be sufficient for diagnosis.
- Adequate immunophenotyping to establish diagnosis\(^c,d\)
  - IHC panel: For high clinical suspicion of NKTL, first panel should include: cCD3ɛ, CD56, EBER-ISH\(^e\)

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Molecular analysis to detect: TCR gene rearrangement
- IHC panel:
  - B-cell lineage: CD20
  - T-cell lineage: CD2, CD7, CD8, CD4, CD5
  - Other: CD30, Ki-67

\(^a\)It is preferred that treatment occur at centers with expertise in the management of this disease.
\(^b\)Necrosis is very common in diagnostic biopsies and may delay diagnosis significantly. Biopsy should include the edges of lesions to increase the odds of having viable tissue. Useful to perform multiple nasopharyngeal biopsies even in areas not clearly involved.
\(^c\)See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (See B-cell Lymphomas Guidelines)
\(^d\)Typical NK-Cell immunophenotype: CD20+, CD2-, cCD3ɛ+ (surface CD3-), CD4-, CD5-, CD7+/-, CD8+/-, CD43+, CD45RO+, CD56+, T-cell receptor (TCR) αβ-, TCRγδ-, EBV- EBER+. TCR and Ig genes are germine (NK lineage). Cytotoxic granule proteins (TIA1, Perforin, Granzyme B) are usually expressed. Typical T-cell immunophenotype: CD2+ sCD3+ cCD3e+, CD4, 5, 7, 8 variable, CD56+/- EBV-EBER+ TCRαβ or γδ+, cytotoxic granule proteins +. TCR genes are clonally rearranged.

### WORKUP

**ESSENTIAL:**
- Physical exam: attention to complete ENT evaluation nasopharynx involvement (including Waldeyer's ring), testicles, and skin
- Performance status
- B symptoms
- CBC, differential platelets
- LDH
- Comprehensive metabolic panel
- Uric acid
- Bone marrow biopsy + aspirate\(^f\)
- Chest/abdominal/pelvic CT with contrast of diagnostic quality and/or PET/CT scan
- Dedicated CT or MRI of the nasal cavity, hard palate, anterior fossa, nasopharynx
- Calculation of Prognostic Index of Natural Killer Lymphoma (PINK)\(^g\)
- Echocardiogram or MUGA scan if treatment includes regimens containing anthracyclines or anthrancenedione
- EBV viral load\(^h\)
- Concurrent referral to RT for pre-treatment evaluation

**USEFUL IN SELECTED CASES:**
- Pregnancy testing in women of child-bearing age (if chemotherapy or RT planned)
- Discussion of fertility and sperm banking
- HIV testing

\(^e\)Negative result should prompt pathology review for alternative diagnosis.
\(^f\)BM aspirate - lymphoid aggregates are rare, and are considered involved if EBER-1 positive; hemopagocytosis may be present.
\(^g\)See Prognostic Index of Natural Killer Lymphoma (PINK) (NKTL-A)
\(^h\)EBV viral load is important in diagnosis and possibly in monitoring of disease. A positive result is consistent with NK/T-cell, nasal type. Lack of normalization of EBV viremia should be considered indirect evidence of persistent disease.

### SUBTYPES

- **Subtypes included:**
  - Extranodal NK/T-cell, nasal type
- **Subtypes not included:**
  - NK-cell leukemias
  - Precursor NK-cell neoplasm

### Note:
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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Extranodal NK/T-Cell Lymphoma, nasal type

**STAGE**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Performance status</th>
</tr>
</thead>
<tbody>
<tr>
<td>I, II</td>
<td>Unfit for chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Clinical trial or RT alone</td>
</tr>
<tr>
<td>IV</td>
<td>Fit for chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Clinical trial or Concurrent chemoradiation or Sequential chemoradiation or Sandwich chemoradiation in selected patients</td>
</tr>
<tr>
<td></td>
<td>Clinical trial or Concurrent chemoradiation or Combination chemotherapy regimen (pegaspargase-based) ± RT</td>
</tr>
</tbody>
</table>

**INDUCTION THERAPY**

- Nasal
  - Stage I, II: Clinical trial or RT alone
  - Stage IV: Clinical trial or Concurrent chemoradiation or Sequential chemoradiation or Sandwich chemoradiation in selected patients
- Extranasal: Clinical trial or Concurrent chemoradiation or Combination chemotherapy regimen (pegaspargase-based) ± RT

Consider prophylaxis for tumor lysis syndrome *(See LYMPH-A)*

*It is preferred that treatment occur at centers with expertise in the management of this disease.*

*In rare circumstances of stage I primary cutaneous NK/T-cell lymphoma, IFRT for solitary skin lesions can be considered.*

*See Suggested Treatment Regimens (NKTL-B).*

**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Extranodal NK/T-Cell Lymphoma, nasal type

**POST RT EVALUATION**

- Repeat initial imaging of CT, MRI, or PET/CT scan
- Endoscopy with visual inspection and repeat biopsies
- EBV viral load

**RESPONSE TO THERAPY**

- CR → Observe
- Negative → Clinical trial or Second-line chemotherapy → HSCT, if eligible
- Positive → Refractory disease → Clinical trial or Second-line chemotherapy → HSCT, if eligible

**ADDITIONAL THERAPY**

- PR → Biopsy
- Negative → Clinical trial or Second-line chemotherapy → HSCT, if eligible
- Positive → Refractory disease → Clinical trial or Second-line chemotherapy → HSCT, if eligible

**Stage I, II**

- Nasal

**Stage IV**

- Extranasal

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### PROGNOSTIC INDEX OF NATURAL KILLER CELL LYMPHOMA (PINK)\(^a\)

<table>
<thead>
<tr>
<th>RISK FACTORS</th>
<th>Number of risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;60 y</td>
<td>0</td>
</tr>
<tr>
<td>Stage III or IV disease</td>
<td>1</td>
</tr>
<tr>
<td>Distant lymph-node involvement</td>
<td>&gt;2</td>
</tr>
</tbody>
</table>


### PROGNOSTIC INDEX OF NATURAL KILLER CELL LYMPHOMA WITH EPSTEIN-BARR VIRUS DNA (PINK-E)\(^a\)

<table>
<thead>
<tr>
<th>RISK FACTORS</th>
<th>Number of risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;60 y</td>
<td>0-1</td>
</tr>
<tr>
<td>Stage III or IV disease</td>
<td>2</td>
</tr>
<tr>
<td>Distant lymph-node involvement</td>
<td>&gt;3</td>
</tr>
</tbody>
</table>

Extranodal NK/T-Cell Lymphoma, nasal type

SUGGESTED TREATMENT REGIMENS

(in alphabetical order)

Combination chemotherapy regimen (pegaspargase-based)
- AspaMetDex (pegaspargase, methotrexate, and dexamethasone) (Reported as a second-line regimen)
- SMILE (steroid [dexamethasone], methotrexate, ifosfamide, pegaspargase, and etoposide) x 4–6 cycles for advanced stage
- GELOX (gemcitabine, pegaspargase, and oxaliplatin)

Concurrent chemoradiation therapy (CCRT)
- RT 50 Gy and 3 courses of DeVIC (dexamethasone, etoposide, ifosfamide, and carboplatin)
- RT 40–52.8 Gy and cisplatin followed by 3 cycles of VIPD (etoposide, ifosfamide, cisplatin, and dexamethasone)

Sequential chemoradiation
- For Stage I, II, SMILE followed by RT 45–50.4 Gy x 2–4 cycles

Sandwich chemoradiation
- GELOX x 2 cycles followed by RT 56 Gy followed by GELOX x 2–4 cycles

Radiation therapy alone (unfit for chemotherapy)
- Recommended tumor dose is ≥50 Gy
  - Early or up-front RT had an essential role in improved OS and DFS in patients with localized extranodal NK/T-cell lymphoma, nasal-type, in the upper aerodigestive tract.
  - Up-front RT may yield more benefits on survival in patients with stage I disease.

See references for regimens NKTL-B 2 of 2.

Pegaspargase-based regimens are preferred. However, there are no data to recommend one particular regimen over another. Treatment should be individualized based on patient's tolerance and comorbidities. GELOX is an option for selected patients who cannot tolerate intense chemotherapy.
SUGGESTED TREATMENT REGIMENS

Combination Chemotherapy Regimen


Concurrent Chemoradiotherapy


Sandwich Chemoradioradiation


Radiation Therapy Alone

References

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Tumor Lysis Syndrome (TLS)

- Laboratory hallmarks of TLS:
  - High potassium
  - High uric acid
  - High phosphorous
  - Low calcium

- Symptoms of TLS:
  - Nausea and vomiting, shortness of breath, irregular heartbeat, clouding of urine, lethargy, and/or joint discomfort.

- High-risk features
  - Histologies of Burkitt lymphoma and lymphoblastic lymphoma; occasionally patients with DLBCL and CLL
  - Spontaneous TLS
  - Elevated WBC
  - Bone marrow involvement
  - Pre-existing elevated uric acid
  - Ineffectiveness of allopurinol
  - Renal disease or renal involvement by tumor

- Treatment of TLS:
  - TLS is best managed if anticipated and treatment is started prior to chemotherapy.
  - Centerpiece of treatment includes
    - Rigorous hydration
    - Management of hyperuricemia
    - Frequent monitoring of electrolytes and aggressive correction is essential
  - First-line and at retreatment for hyperuricemia
    - Allopurinol beginning 2–3 days prior to chemotherapy and continued for 10–14 days
    - Rasburicase is indicated for patients with any of the following risk factors:
      - presence of any high-risk feature
      - urgent need to initiate therapy in a high-bulk patient
      - situations where adequate hydration may be difficult or impossible
      - Acute renal failure
    - One dose of rasburicase is frequently adequate. Doses of 3–6 mg are usually effective.\(^a\) Redosing should be individualized.
  - If TLS is untreated, its progression may cause acute kidney failure, cardiac arrhythmias, seizures, loss of muscle control, and death.

\(^a\)There are data to support that fixed-dose rasburicase is very effective in adult patients.
SUPPORTIVE CARE

For other immunosuppressive situations, see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

Monoclonal Antibody Therapy and Viral Reactivation

_Brentuximab Vedotin (anti-CD30 antibody-drug conjugate)_

Progressive multifocal leukoencephalopathy (PML):
- Caused by the JC virus and is usually fatal.
  - Diagnosis made by PCR of CSF and in some cases brain biopsy.
- No known effective treatment.
- Clinical indications may include changes in behavior such as confusion, dizziness or loss of balance, difficulty talking or walking, and vision problems.

_Anti-CD52 Antibody Therapy: Alemtuzumab_

Cytomegalovirus (CMV) reactivation:
- The current appropriate management is controversial; some NCCN Member Institutions use ganciclovir (oral or IV) preemptively if viremia is present, others only if viral load is rising.
- CMV viremia should be measured by quantitative PCR at least every 2 to 3 weeks.
- Consultation with an infectious disease expert may be necessary. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

Renal Dysfunction Associated with Methotrexate
- Consider use of glucarpidase if significant renal dysfunction and methotrexate levels are >10 microM beyond 42 to 48 hours. Leucovorin remains a component in the treatment of methotrexate toxicity and should be continued for at least 2 days following glucarpidase administration. However, be aware that leucovorin is a substrate for glucarpidase, and therefore should not be administered within two hours prior to or following glucarpidase.

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# LUGANO RESPONSE CRITERIA FOR NON-HODGKIN’S LYMPHOMA

PET should be done with contrast-enhanced diagnostic CT and can be done simultaneously or at separate procedures.

<table>
<thead>
<tr>
<th>Response</th>
<th>Site</th>
<th>PET-CT (Metabolic response)</th>
<th>CT (Radiologic response)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete response</strong></td>
<td>Lymph nodes and extralymphatic sites</td>
<td>Score 1, 2, or 3&lt;sup&gt;a&lt;/sup&gt; with or without a residual mass on 5 point scale (5-PS)&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>All of the following: Target nodes/nodal masses must regress to ≤1.5 cm in longest transverse diameter of a lesion (LDi) No extralymphatic sites of disease</td>
</tr>
<tr>
<td>Non-measured lesion</td>
<td>Not applicable</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>Organ enlargement</td>
<td>Not applicable</td>
<td>Regress to normal</td>
<td></td>
</tr>
<tr>
<td>New Lesions</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Bone Marrow</td>
<td>No evidence of FDG-avid disease in marrow</td>
<td>Normal by morphology; if indeterminate, and flow cytometry IHC negative</td>
<td></td>
</tr>
</tbody>
</table>

| **Partial response** | Lymph nodes and extralymphatic sites | Score 4 or 5<sup>b</sup> with reduced uptake compared with baseline. No new or progressive lesions. At interim these findings suggest responding disease. At end of treatment these findings may indicate residual disease. | All of the following: 
≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites. When a lesion is too small to measure on CT, assign 5mm x 5mm as the default value. When no longer visible, 0x0 mm For a node >5mm x 5mm, but smaller than normal, use actual measurement for calculation |
| Non-measured lesion | Not applicable | Absent/normal, regressed, but no increase |
| Organ enlargement | Not applicable | Spleen must have regressed by >50% in length beyond normal |
| New Lesions | None | None |
| Bone Marrow | Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consider further evaluation with biopsy, or an interval scan. | Not applicable |

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Footnotes on LYMP-B 3 of 3

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# LUGANO RESPONSE CRITERIA FOR NON-HODGKIN'S LYMPHOMA

PET should be done with contrast-enhanced diagnostic CT and can be done simultaneously or at separate procedures.

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<th>Site</th>
<th>PET-CT (Metabolic response)</th>
<th>CT (Radiologic response)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No response or stable disease</td>
<td>Target nodes/nodal masses, extranodal lesions</td>
<td>Score 4 or 5&lt;sup&gt;b&lt;/sup&gt; with no significant change in FDG uptake from baseline at interim or end of treatment. No new or progressive lesions</td>
<td>&lt;50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met</td>
</tr>
<tr>
<td></td>
<td>Non-measured lesion</td>
<td>Not applicable</td>
<td>No increase consistent with progression</td>
</tr>
<tr>
<td></td>
<td>Organ enlargement</td>
<td>Not applicable</td>
<td>No increase consistent with progression</td>
</tr>
<tr>
<td></td>
<td>New Lesions</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Bone Marrow</td>
<td>No change from baseline</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>Individual target nodes/nodal masses Extranodal lesions</td>
<td>Score 4 or 5&lt;sup&gt;b&lt;/sup&gt; with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Requires at least one of the following PPD progression: An individual node/lesion must be abnormal with: LDi &gt;1.5 cm and Increase by ≥50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions &gt;2 cm In the setting of splenomegaly, the splenic length must increase by &gt;50% of the extent of its prior increase beyond baseline. If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly</td>
</tr>
<tr>
<td></td>
<td>Non-measured lesion</td>
<td>None</td>
<td>New or clear progression of preexisting nonmeasured lesions</td>
</tr>
<tr>
<td></td>
<td>New Lesions</td>
<td>New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Regrowth of previously resolved lesions A new node &gt;1.5 cm in any axis A new extranodal site &gt;1.0 cm in any axis; if &lt;1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma</td>
</tr>
<tr>
<td></td>
<td>Bone Marrow</td>
<td>New or recurrent FDG-avid foci</td>
<td>New or recurrent involvement</td>
</tr>
</tbody>
</table>


Footnotes on LYMP-B 3 of 3

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LUGANO RESPONSE CRITERIA FOR NON-HODGKIN’S LYMPHOMA

Footnotes

a Score 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider score 3 as an inadequate response (to avoid under-treatment).

b See PET Five Point Scale (5-PS).

c It is recognized that in Waldeyer’s ring or extranodal sites with high physiological uptake or with activation within spleen or marrow, e.g. with chemotherapy or myeloid colony stimulating factors, uptake may be greater than normal mediastinum and/or liver. In this circumstance, CMR may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiological uptake.

d FDG-avid lymphomas should have response assessed by PET-CT. Diseases that can typically be followed with CT alone include CLL/SLL and marginal zone lymphomas.

e False-positive PET scans may be observed related to infectious or inflammatory conditions. Biopsy of affected sites remains the gold standard for confirming new or persistent disease at end of therapy.

PET Five Point Scale (5-PS)

1 No uptake above background
2 Uptake ≤ mediastinum
3 Uptake > mediastinum but ≤ liver
4 Uptake moderately > liver
5 Uptake markedly higher than liver and/or new lesions
X New areas of uptake unlikely to be related to lymphoma

SPD – sum of the product of the perpendicular diameters for multiple lesions
LDi – Longest transverse diameter of a lesion
SDi – Shortest axis perpendicular to the LDi
PPD – Cross product of the LDi and perpendicular diameter

Measured dominant lesions – Up to 6 of the largest dominant nodes, nodal masses and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body, and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs, e.g., liver, spleen, kidneys, lungs, etc, gastrointestinal involvement, cutaneous lesions of those noted on palpation. Non-measured lesions – Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant, measurable or which do not meet the requirements for measurability, but are still considered abnormal. As well as truly assessable disease which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses and other lesions that cannot be confirmed and followed by imaging.

PRINCIPLES OF RADIATION THERAPY

- Treatment with photons, electrons, or protons may all be appropriate, depending on clinical circumstances.
- Advanced radiation therapy technologies such as IMRT, breath hold or respiratory gating, image-guided therapy, or proton therapy may offer significant and clinically relevant advantages in specific instances to spare important organs at risk such as the heart (including coronary arteries and valves), lungs, kidneys, spinal cord, esophagus, bone marrow, breasts, stomach, muscle/soft tissue, and salivary glands and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control. Achieving highly conformal dose distributions is especially important for patients who are being treated with curative intent or who have long life expectancies following therapy.
- The demonstration of significant dose-sparing for these organs at risk reflects best clinical practice.
- In mediastinal lymphoma, the use of 4D-CT for simulation and the adoption of strategies to deal with respiratory motion such as inspiration breath-hold techniques, and image-guided RT during treatment delivery is also important.
- Since the advantages of these techniques include tightly conformal doses and steep gradients next to normal tissues, target definition and delineation and treatment delivery verification require careful monitoring to avoid the risk of tumor geographic miss and subsequent decrease in tumor control. Image guidance may be required to provide this assurance.
- Randomized studies to test these concepts are unlikely to be done since these techniques are designed to decrease late effects, which take 10+ years to evolve. In light of that, the modalities and techniques that are found to best reduce the doses to the organs at risk (OAR) in a clinically meaningful way without compromising target coverage should be considered.

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See references on LYMP-C 4 of 4.
PRINCIPLES OF RADIATION THERAPY

Volumes:

- **Involved-site radiation therapy (ISRT) for nodal disease**
  
  ISRT is recommended as the appropriate field for NHL. Planning for ISRT requires modern CT-based simulation and planning capabilities. Incorporating other modern imaging like PET and MRI often enhances treatment volume determination.
  
  ISRT targets the site of the originally involved lymph node(s). The volume encompasses the original suspicious volume prior to chemotherapy or surgery. Yet, it spares adjacent uninvolved organs (like lungs, bone, muscle, or kidney) when lymphadenopathy regresses following chemotherapy.
  
  The pre-chemotherapy or pre-biopsy gross tumor volume (GTV) provides the basis for determining the clinical target volume (CTV). Concerns for questionable subclinical disease and uncertainties in original imaging accuracy or localization may lead to expansion of the CTV and are determined individually using clinical judgment.
  
  For indolent NHL, often treated with RT alone, larger fields should be considered. For example, the CTV definition for treating follicular lymphoma with radiation therapy alone will be greater than that employed for DLBCL with similar disease distribution being treated with combined modality therapy.
  
  Possible movement of the target by respiration as determined by 4D-CT or fluoroscopy (internal target volume- ITV) should also influence the final CTV.
  
  The planning treatment volume (PTV) is an additional expansion of the CTV that accounts only for setup variations (see ICRU definitions).
  
  The OAR should be outlined for optimizing treatment plan decisions.
  
  The treatment plan is designed using conventional, 3-D conformal, or IMRT techniques using clinical treatment planning considerations of coverage and dose reductions for OAR.

- **ISRT for extranodal disease**
  
  Similar principles as for ISRT nodal sites (see above).
  
  For most organs and particularly for indolent disease, the whole organ comprises the CTV (eg, stomach, salivary gland, thyroid). For other organs, including orbit, breast, lung, bone, localized skin, and in some cases when RT is consolidation after chemotherapy, partial organ RT may be appropriate.
  
  For most NHL subtypes no radiation is required for uninvolved lymph nodes.

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\(^a\)See references on [LYMP-C 4 of 4](#).

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

PRINCIPLES OF RADIATION THERAPY

General Dose Guidelines:

• PTCL
  ▶ Consolidation after chemotherapy CR: 30–36 Gy
  ▶ Complementary after PR: 40–50 Gy
  ▶ RT as primary treatment for refractory or non-candidates for chemotherapy: 40–55 Gy
  ▶ In combination with stem cell transplantation: 20–36 Gy, depending on sites of disease and prior RT exposure

• NK-T cell lymphoma
  ▶ RT as primary treatment 50–55 Gy
  ▶ RT in combined modality therapy 45–50.4 Gy
• Primary cutaneous anaplastic large cell lymphoma: 30–36 Gy

See references on LYMP-C 4 of 4.
PRINCIPLES OF RADIATION THERAPY

REFERENCES


# Table 1

**WHO Classification of the Mature B-Cell, T-Cell, and NK-Cell Neoplasms (2016)**

### Mature B-Cell Neoplasms

- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- Monoclonal B-cell lymphocytosis
- B-cell prolymphocytic leukemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- *Splenic lymphoma/leukemia, unclassifiable*
  - *Splenic diffuse red pulp small B-cell lymphoma*
  - *Hairy cell leukemia-variant*
- Lymphoplasmacytic lymphoma
- Waldenström’s macroglobulinemia
- Monoclonal gammopathy of undetermined significance (MGUS), IgM
- Mu heavy chain disease
- Gamma heavy chain disease
- Alpha heavy chain disease
- Monoclonal gammopathy of undetermined significance (MGUS), IgG/A
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extraosseous plasmacytoma
- Monoclonal immunoglobulin deposition diseases
- Extramedullary marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT type)
- Nodal marginal zone lymphoma
  - *Pediatric nodal marginal zone lymphoma*
- Follicular lymphoma
  - In situ follicular neoplasia
  - Duodenal-type follicular lymphoma
- Pediatric-type follicular lymphoma
- Large B-cell lymphoma with IRF4 rearrangement
- Primary cutaneous follicle center lymphoma
- Mantle cell lymphoma
  - In situ mantle cell neoplasia
- Diffuse large B-cell lymphoma (DLBCL), NOS
  - Germinal center B-cell type
  - Activated B-cell type
- T-cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the central nervous system (CNS)
- Primary cutaneous DLBCL, leg type
- EBV-positive DLBCL, NOS
- *EBV-positive mucocutaneous ulcer*
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK-positive large B-cell lymphoma
- Plasmablastic lymphoma
- Primary effusion lymphoma
- *HHV8-positive DLBCL, NOS*
- Burkitt lymphoma
- *Burkitt-like lymphoma with 11q aberration*
- High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements
- High-grade B-cell lymphoma, NOS
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

*Provisional entities are listed in italics.  

[Continued on next page]
## Classification

### WHO Classification of the Mature B-Cell, T-Cell, and NK-Cell Neoplasms (2016)

#### Mature T-Cell and NK-Cell Neoplasms
- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- *Chronic lymphoproliferative disorder of NK-cells*
- Aggressive NK-cell leukemia
- Systemic EBV-positive T-cell lymphoma of childhood
- Hydroa vacciniforme–like lymphoproliferative disorder
- Adult T-cell leukemia/lymphoma
- Extramedullary T/NK-cell lymphoma
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma*
- *Indolent T-cell lymphoproliferative disorder of the GI tract*
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30-positive T-cell lymphoproliferative disorders
  - Lymphomatoid papulosis
  - Primary cutaneous gamma-delta T-cell lymphoma
- Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma*
- Primary cutaneous acral CD8-positive T-cell lymphoma*
- Primary cutaneous CD4-positive small/medium T-cell lymphoproliferative disorder*
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Follicular T-cell lymphoma*
- Nodal peripheral T-cell lymphoma with TFH phenotype*
- Anaplastic large-cell lymphoma, ALK positive
- Anaplastic large-cell lymphoma, ALK negative
- Breast implant–associated anaplastic large-cell lymphoma*

#### Hodgkin Lymphoma
- Nodular lymphocyte-predominant Hodgkin lymphoma
- Classical Hodgkin lymphoma
  - Nodular sclerosis classical Hodgkin lymphoma
  - Lymphocyte-rich classical Hodgkin lymphoma
  - Mixed cellularity classical Hodgkin lymphoma
  - Lymphocyte-depleted classical Hodgkin lymphoma

#### Posttransplant Lymphoproliferative Disorders (PTLD)
- Plasmacytic hyperplasia PTLD
- Infectious mononucleosis-like PTLD
- Florid follicular hyperplasia PTLD
- Polymorphic PTLD
- Monomorphic PTLD (B- and T/NK-cell types)
- Classical Hodgkin lymphoma PTLD

#### Histiocytic and dendritic cell neoplasms
- Histiocytic sarcoma
- Langerhans cell histiocytosis
- Langerhans cell sarcoma
- Indeterminate dendritic cell tumor
- Interdigitating dendritic cell sarcoma
- Follicular dendritic cell sarcoma
- Fibroblastic reticular cell tumor
- Disseminated juvenile xanthogranuloma
- Erdheim-Chester disease

*Provisional entities are listed in italics.

### Staging

#### Lugano Modification of Ann Arbor Staging System*
(for primary nodal lymphomas)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Involvement</th>
<th>Extranodal (E) status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Limited</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>One node or a group of adjacent nodes</td>
<td>Single extranodal lesions without nodal involvement</td>
</tr>
<tr>
<td>Stage II</td>
<td>Two or more nodal groups on the same side of the diaphragm</td>
<td>Stage I or II by nodal extent with limited contiguous extranodal involvement</td>
</tr>
<tr>
<td>Stage II bulky**</td>
<td>II as above with “bulky” disease</td>
<td>Not applicable</td>
</tr>
<tr>
<td><strong>Advanced</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>Nodes on both sides of the diaphragm</td>
<td>Not applicable</td>
</tr>
<tr>
<td></td>
<td>Nodes above the diaphragm with spleen involvement</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>Additional non-contiguous extralymphatic involvement</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

*Extent of disease is determined by PET/CT for avid lymphomas, and CT for non-avid histologies

Note: Tonsils, Waldeyer’s ring, and spleen are considered nodal tissue

**Whether II bulky is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

Categorization of A versus B has been removed from the Lugano Modification of Ann Arbor Staging.

NCCN Guidelines Version 2.2017
T-cell Lymphomas

Discussion
This discussion is being updated to correspond with the newly updated algorithm. Last updated on 05/03/16

NCCN Categories of Evidence and Consensus

**Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

**Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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Overview

Non-Hodgkin’s lymphomas (NHL) are a heterogeneous group of lymphoproliferative disorders originating in B-lymphocytes, T-lymphocytes or natural killer (NK) cells. NK/T-cell lymphomas are very rare. In 2015, an estimated 71,850 people will be diagnosed with NHL and there will be approximately 19,790 deaths due to the disease. Cases of chronic lymphocytic leukemia (CLL) are estimated separately. NHL is the seventh leading site of new cancer cases among men and women, accounting for 4% of new cancer cases and 3% of cancer-related deaths. In a prospectively collected data from the National Cancer Data Base, diffuse large B-cell lymphoma (DLBCL; 32.5%), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL; 18.6%), follicular lymphoma (FL; 17.1%), marginal zone lymphomas (MZL; 8.3%), mantle cell lymphoma (MCL; 4.1%) and peripheral T-cell lymphoma not-otherwise-specified (PTCL-NOS; 1.7%) were the major subtypes of NHL diagnosed in the United States between 1998-2011.

The incidence of NHL has increased dramatically between 1970 and 1995; the increase has moderated since the mid-90s. This increase has been attributed partly to the human immunodeficiency virus (HIV) epidemic and the development of AIDS-related NHL. However, much of the increase in incidence has been observed in patients in their sixth and seventh decades; a large part of this increase incidence has paralleled a major decrease in mortality from other causes. The median age of individuals with NHL has risen in the last two decades. As a result, patients with NHL may also have significant comorbid conditions, which complicate treatment options.

The National Comprehensive Cancer Network (NCCN®) Guidelines (NCCN Guidelines®) were developed as a result of meetings convened by a multidisciplinary panel of NHL experts, with the aim to provide recommendations for diagnostic workup, treatment, and surveillance strategies for the most common subtypes of NHL, in addition to a general discussion on the classification systems used in NHL and supportive care considerations.

The most common B-cell Lymphoma subtypes that are covered in these NCCN Guidelines are listed below:

- Peripheral T-cell lymphomas (PTCL)
- Breast Implant-associated ALCL
- Mycosis fungoides (MF) and Sezary syndrome(SS)
- Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders
- T-cell Large Granular Lymphocytic Leukemia
- Adult T-cell leukemia/lymphoma (ATLL)
- T-cell prolymphocytic leukemia (T-PLL)
- Extranodal NK/T-cell lymphomas, nasal type (ENKL)

Classification

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

**International Working Formulation Classification**

The IWF classified NHL into three major categories as low, intermediate and high grade, based on the morphology and natural history. This classification divided DLBCL into intermediate and high grade groups. However, these distinctions were not reproducible. Since this classification did not include immunophenotyping, the categories were not reproducible. In addition, after this classification was published, many new diseases were described that were not included in the IWF classification.

**Revised European American Classification**

In 1994, the International Lymphoma Study Group (ILSG) developed the REAL classification, which classified lymphomas based on the cell of origin (B, T, or NK) and included morphology, immunophenotype, genetic and clinical features to define diseases. In 1997, the International Lymphoma Classification Project performed a clinical evaluation of the Revised European American Classification (REAL) classification in a cohort of 1,403 cases of NHL. The diagnosis of NHL was confirmed in 1,378 (98.2%) of the cases. This study identified the thirteen most common histological types, comprising about 90% of the cases of NHL in the United States. The findings were as follows: DLBCL, 31%; follicular lymphoma (FL), 22%; small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL), 6%; mantle cell lymphoma (MCL), 6%; peripheral T-cell lymphoma (PTCL), 6%; and mucosa associated lymphoid tissue (MALT) lymphoma, 5%. The remaining subtypes each occurred in less than 2% of cases. Importantly, in the United States more than 50% of cases of lymphoma are either DLBCL or FL. The study investigators concluded that the REAL classification can be readily applied and identifies clinically distinctive types of NHL.

**World Health Organization Classification**

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

In 2008, the International T-cell lymphoma Project evaluated the WHO classification of T-cell lymphoma in a cohort of 1,314 cases of PTCL and natural killer/T-cell lymphomas (NKTCL). The diagnosis of PTCL or NKTCL was confirmed in 1,153 cases (88%). The most common subtypes were PTCL-not otherwise specified (NOS; 25.9%), angioimmunoblastic lymphoma (18.5%), NKTCL (10.4%), adult T-cell leukemia/lymphoma (ATLL; 9.6%), anaplastic large cell lymphoma (ALCL), ALK-positive (6.6%) and ALCL, ALK-negative (5.5%). The findings of this study validated the utility of the WHO classification for defining subtypes of T-cell lymphomas.

The WHO classification was updated again in September 2008 to add new diseases and subtypes that have been recognized in the past decade, and to better define some of the heterogeneous and ambiguous categories based on the recent advances. Genetic
features, detected by cytogenetics or fluorescence in-situ hybridization (FISH) are increasingly important in defining specific NHL subtypes. In addition, detection of viruses, particularly Epstein-Barr virus, HHV8 and HTLV1, is often necessary to establish a specific diagnosis.

**2008 WHO Classification of Mature T-cell and NK-cell Lymphomas**

The 2008 WHO classification has adapted the EOTRC classification for cutaneous T-cell lymphomas. The new categories include primary cutaneous gamma-delta T-cell lymphoma, primary cutaneous aggressive epidermotropic CD9-positive cytotoxic T-cell lymphoma and primary cutaneous small/medium CDE4-positive T-cell lymphoma. Anaplastic large cell lymphoma (ALCL), ALK-negative is now separated out from PTCL-NOS as a provisional entity.

**ALCL**

ALCL accounts for less than 5% of all cases of NHL. There are now three distinctly recognized subtypes of ALCL: ALCL, ALK-positive, ALCL, ALK-negative and primary cutaneous ALCL. Primary cutaneous ALCL is a distinct subtype of mature T-cell lymphoma. ALK-positive ALCL is most common in children and young adults. It is characterized by the over expression of anaplastic lymphoma kinase (ALK1) protein, resulting from t(2;5) in 40-60% of patients. Although clinically aggressive, it is highly curable with CHOP chemotherapy. The distinction between ALK-positive and ALK-negative ALCL was not required in the 2001 WHO classification. It is now clear that ALK-positive ALCL is a well-defined clinicopathologic entity. The International Peripheral T-Cell Lymphoma Project reported that patients with ALK-positive ALCL had a superior outcome compared with those with ALK-negative ALCL [5-year failure-free survival (FFS): 60% vs. 36%; and 5-year overall survival (OS): 70% vs. 49%]. Contrary to prior reports, ALK-negative ALCL was associated with a better outcome than PTCL-NOS. The 5-year FFS (36% vs. 20%) and OS (49% vs. 32%) were superior compared with PTCL-NOS. A recent analysis from the GELA found that age and beta-2 microglobulin, not ALK1 expression, were the most significant prognostic factors of overall survival for patients with ALCL; however, age was very closely associated with ALK1 expression. Patients with primary cutaneous ALCL had a very favorable 5-year OS (90%) despite being negative for ALK1; the 5-year FFS rate was 55%. The findings of this study confirmed that ALK-negative ALCL should be separated from both ALK-positive ALCL and PTCL-NOS. Based on the recent findings, the 2008 WHO classification has included a provisional category for ALK-negative ALCL. It is morphologically identical to ALK-positive ALCL, with a strong and diffuse expression of CD30, no expression of B-cell antigens and absence of ALK1. The prognosis is intermediate between that of ALK-positive ALCL and PTCL-NOS.

**Response Assessment**

The International Working Group (IWG) published the guidelines for response criteria for lymphoma in 1999. These response criteria are based on the reduction in the size of the enlarged lymph node as measured by CT scan and the extent of bone marrow involvement that is determined by bone marrow aspirate and biopsy. These guidelines were revised in 2007 by the International Harmonization Project to incorporate IHC, flow cytometry and 18-flourodeoxyglucose (FDG)-positron emission tomography (PET) scans in the definition of response for lymphoma. In the revised guidelines, the response category of complete response uncertain (CRu) was essentially eliminated because residual masses were defined as a partial response (PR) or a complete response (CR) based on the result of a PET scan. The response is categorized as CR, PR, stable disease (SD) and relapsed disease or progressive disease (PD).
In 2014, revised response criteria, known as the Lugano criteria, were introduced for staging and response assessment using PET-CT scans.25,26 PET-CT is recommended for initial staging of all FDG-avid lymphomas. The use of 5-point scale (5-PS) is recommended for the interpretation and reporting of PET-CT scans. The 5-PS is based on the visual assessment of FDG uptake in the involved sites relative to that of the mediastinum and the liver.27-29 A score of 1 denotes no abnormal FDG-avidity, while a score of 2 represents uptake less than the mediastinum. A score of 3 denotes uptake greater than the mediastinum but less than the liver, while scores of 4 and 5 denote uptake greater than the liver, and greater than the liver with new sites of disease, respectively. Different clinical trials have considered scores of either 1-2 or 1-3 to be PET-negative, while scores of 4-5 are universally considered PET-positive. A score of 4 on an interim or end of treatment restaging scan may be consistent with a partial response if the FDG-avidity has declined from initial staging, while a score of 5 denotes progressive disease.

However, the application of PET-CT to response assessment is limited to histologies where there is reliable FDG uptake in active tumor and the revised response criteria have thus far only been validated for DLBCL and Hodgkin lymphoma. The application of the revised response criteria to other histologies requires validation and the original IWG guidelines should be used. Of note, the Lugano response criteria may not be applicable for several of the tumor subtypes included in the NCCN Guidelines. Tumor specific response criteria are included in the guidelines for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), hairy cell leukemia (HCL), mycosis fungoides/Sezary syndrome (MF/SS), adult T-cell leukemia/lymphoma (ATLL), and T-cell-prolymphocytic leukemia (T-PLL).

### Staging

PET-CT scans are now employed for initial staging, restaging and end of treatment response assessment in the majority of patients with NHL.30 In a meta-analysis study, PET showed a high positivity and specificity when used for the staging and restaging of patients with lymphoma.31 PET is nearly universally positive at diagnosis in Hodgkin lymphoma, DLBCL, and follicular lymphoma,32 about 90% in T-cell lymphoma and nodal MZL but less sensitive for extra-nodal MZL.34 However, a number of benign conditions including sarcoid, infection, and inflammation can result in false-positive PET scans, complicating the interpretation. Lesions smaller than 1 cm are not reliably visualized with PET scans. Although PET scans may detect additional disease sites at diagnosis, the clinical stage is modified only in 15-20% of patients and a change in treatment in only 8% of patients. PET scans are now virtually always performed as combined PET-CT scans.

PET-CT has distinct advantages in both staging and restaging compared to full-dose diagnostic CT or PET alone.35,36 In a retrospective study, PET-CT performed with low-dose non-enhanced CT was found to be more sensitive and specific than the routine contrast-enhanced CT in the evaluation of lymph node and organ involvement in patients with Hodgkin disease or high-grade NHL.36 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.35 PET-CT is particularly important for staging before consideration of RT and baseline PET-CT will aid in the interpretation of post-treatment response evaluation based on the 5-PS as described above.26
PET-CT is recommended for initial staging of FDG-avid lymphomas. PET should be done with contrast-enhanced diagnostic CT. Staging imaging with CT is recommended for lymphomas that are minimally FDG-avid (CLL/SLL, marginal zone lymphomas, HCL, cutaneous B-cell lymphomas, MF/SS, CD30+ cutaneous lymphomas and T-cell large granular lymphocytic leukemia), except in selected circumstances. FDG-avid lymphomas should have response assessed by PET-CT using the 5-PS. False-positive PET scans may be observed related to infectious or inflammatory conditions. Biopsy of affected sites remains the gold standard for confirming new or persistent disease at end of therapy.

**Principles of Radiation Therapy**

Radiation therapy (RT) can be delivered with photons, electrons or protons, depending upon clinical circumstances. Advanced RT techniques emphasize tightly conformal doses and steep gradients next to normal tissues. Therefore, target definition and delineation and treatment delivery verification require careful monitoring to avoid the risk of missing geographic location of the tumor and subsequent decrease in tumor control. Image guidance may be required to facilitate target definition. Preliminary results from single-institution studies have shown that significant dose reduction to organs at risk (OAR; eg, lungs, heart, breasts, kidneys, spinal cord, esophagus, carotid artery, bone marrow, stomach, muscle, soft tissue and salivary glands) can be achieved with advanced RT planning and delivery techniques such as 4D-CT simulation, intensity-modulated RT (IMRT), image-guided RT, respiratory gating or deep inspiration breath hold. These techniques offer significant and clinically relevant advantages in specific instances to spare OAR and decrease the risk for normal tissue damage and late effects without compromising the primary goal of local tumor control.

In mediastinal lymphoma, the use of 4D-CT simulation and the adoption of strategies to deal with respiratory motion such as inspiration breath-hold techniques, and image guided RT during treatment delivery is also important.

Randomized prospective studies to test these concepts are unlikely to be done since these techniques are designed to decrease late effects, which usually develop ≥ 10 years after completion of treatment. Therefore, the guidelines recommend that RT delivery techniques that are found to be best reduce the doses to the OAR in a clinically meaningful manner without compromising target coverage should be considered.

Involved-site RT (ISRT) is intended to limit radiation exposure to adjacent uninvolved organs (such as lungs, bone, muscle, or kidney) when lymphadenopathy regresses following chemotherapy, thus minimizing the potential long term complications. Extended-field RT (EFRT) and involved-field RT (IFRT) techniques have now been replaced by ISRT, in an effort to restrict the size of the RT fields to smaller volumes. ISRT targets the initially involved nodal and extra-nodal sites detectable at presentation. Larger RT fields should be considered for limited stage indolent NHL, often treated with RT alone.

Treatment planning for ISRT requires the use of CT-based simulation. The incorporation of additional imaging techniques such as PET and MRI often enhances the treatment planning. The OAR should be outlined for optimizing treatment plan decisions. The treatment plan is designed using conventional, 3D conformal, or IMRT techniques using clinical treatment planning considerations of coverage and dose reductions for OAR.

The principles of ISRT are similar for both nodal and extranodal disease. The gross tumor volume (GTV) defined by radiological imaging
prior to biopsy, chemotherapy or surgery provides the basis for determining the clinical target volume (CTV). Possible movement of the target by respiration as determined by 4D-CT or fluoroscopy should also influence the final CTV. The presence of suspected subclinical disease and uncertainties in original imaging accuracy or localization may lead to the expansion of the CTV. The planning treatment volume (PTV) is an additional expansion of the CTV that accounts only for setup variations.

In the case of extranodal disease, particularly for indolent lymphoma, in most cases, the whole organ comprises the CTV (e.g., stomach, salivary gland, and thyroid). For other organs, including orbit, breast, lung, bone, localized skin, and in some cases when RT is consolidation after chemotherapy, partial organ RT may be appropriate. No radiation is required for uninvolved lymph nodes for most NHL subtypes. The general dose guidelines for individual subtypes of NHL are outlined in the “Principles of RT” section of the guidelines.

Diagnosis
In all cases of NHL, the most important first step is an accurate pathologic diagnosis. The basic pathological evaluation is the same in each Guidelines (by tumor subtype), although some further evaluation may be useful in certain circumstances to clarify a particular diagnosis; these are outlined in the pathological evaluation of the individual Guidelines.

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

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

Immunophenotypic analysis is essential for the differentiation of various subtypes of NHL to establish the proper diagnosis. It can be performed by flow cytometry and/or IHC; the choice depends on the antigens as well as the expertise and resources available to the hematopathologist. In some cases flow cytometry and IHC are complementary diagnostic tools. Cytogenetic or molecular genetic analysis may be necessary under certain circumstances to identify the specific chromosomal translocations that are characteristic of some NHL subtypes or to establish clonality.
After the publication of the 2008 WHO Classification, the NHL Guidelines panel developed a series of algorithms for the use of immunophenotyping in the diagnosis of mature lymphoid neoplasms. These algorithms were developed to provide guidance for surgical pathologists as well as an aid to the clinician in the interpretation of pathology reports and they should be used in conjunction with clinical and pathological correlation. See *Immunophenotyping/Genetic Testing* in the guidelines.

**Workup**

Essential workup procedures include a complete physical exam with particular attention to node bearing areas and the size of liver and spleen, symptoms present, performance status, laboratory studies including CBC, serum lactate dehydrogenase (LDH), hepatitis B virus testing (see below), comprehensive metabolic panel, and CT chest/abdominal/pelvic with oral and intravenous contrast (unless co-existent renal insufficiency). MUGA scan or echocardiograms are recommended when anthracyclines and anthracenedione containing regimens are used. Due the risk of hepatitis B reactivation, the panel has included hepatitis B testing (hepatitis B surface antigen and hepatitis B core antibody) as part of essential workup prior to initiation of treatment in all patients who will receive anti CD20 monoclonal antibody-based regimens. Furthermore, hepatitis B reactivation has been reported with chemotherapy alone and testing should be considered in anyone with a risk factor (e.g. blood transfusion, IV drug abuse) or if from a region with a non-negligible prevalence of hepatitis B infection (see “Hepatitis B Reactivation” in the Supportive Care section below). Hepatitis C testing is needed in high-risk patients and patients with splenic marginal zone lymphoma.

Optional procedures (depending on specific lymphoma type) include beta-2-microglobulin, CT or PET-CT scans, endoscopic ultrasound (gastric MALT lymphoma), head CT or brain MRI and lumbar puncture to analyze cerebrospinal fluid (MCL and DLBCL). Discussion of fertility issues and sperm banking should be addressed in the appropriate circumstances.55

Bone marrow biopsy with or without aspirate is essential in all cases where treatment is considered; however, there are circumstances where it may be deferred. Bone marrow biopsy is usually included in the workup for all patients with NHL with the exception of SLL/CLL when there is a clonal lymphocytosis identified by flow cytometry. Bone marrow involvement occurs in 39% of low-grade, 36% of intermediate grade and 18% of high-grade lymphomas. Bone marrow involvement was associated with significantly shorter survivals in patients with intermediate or high-grade lymphomas.56 In a retrospective analysis, the incidence of bone marrow involvement and the parameters predicting bone marrow involvement were analyzed in 192 patients with stage I and II in DLBCL.57 Overall incidence of BM involvement was 3.6%. The authors concluded that bone marrow biopsy may be safely omitted in selected patients with early stage DLBCL.57 In cutaneous B-cell lymphomas, bone marrow biopsy is essential for PC-DLBCL, leg type, since this is an aggressive lymphoma that will probably require systemic treatment, whereas the role of bone marrow biopsy in the PC-FCL and PC-MZL subtypes is less clear. Recent studies have indicated that bone marrow biopsy is an essential component of staging in patients with PC-FCL first presenting in the skin, whereas it appears to have limited value in patients with MZL presenting in the skin, and may be considered only in selected cases.58,59
In the NCCN Guidelines, bone marrow biopsy with or without aspirate is included as part of essential workup for all lymphomas. However, in patients with low bulk indolent disease with radiographic clinical stage III disease, an initial staging bone marrow evaluation can be deferred if observation is recommended as it will not change the clinical recommendations. However, in the evaluation of potentially early stage indolent lymphoma (stage I or II), bone marrow biopsy is essential; some panel members advocate bilateral core biopsies in this situation. Bilateral cores are recommended if radioimmunotherapy is considered.

Supportive Care

Supportive care remains an important component of managing patients with NHL, particularly during active therapy. Supportive care measures for NHL may include (but are not limited to) management of infectious complications, management of tumor lysis syndrome, and use of myeloid growth factors or blood product transfusions. These measures may help to maximize the benefit of NHL therapy for patients by enhancing tolerability, reducing treatment-related toxicities, and ensuring timely delivery of planned treatment courses. Patients with hematologic malignancies are at increased risk for infectious complications due to profound immunosuppression stemming from myelosuppressive therapy and/or the underlying malignancy. For example, reactivation of latent viruses may occur in the setting of significant immunosuppression in patients with NHL.

Viral Reactivation and Infections

Cytomegalovirus Reactivation

Cytomegalovirus (CMV) reactivation may occur among patients with lymphoproliferative malignancies receiving alemtuzumab therapy, and occurs most frequently between 3 to 6 weeks after initiation of therapy when T-cell counts reach a nadir. CMV reactivation is a well-documented infectious complication in patients receiving treatment with alemtuzumab, occurring in up to 25% of treated patients. Current management practices for prevention of CMV reactivation include the use of prophylactic ganciclovir (oral or IV) if CMV viremia is present prior to alemtuzumab therapy, or pre-emptive use of these drugs when the viral load is found to be increasing during therapy.

Patients with hematologic malignancies treated with alemtuzumab-containing regimens should be closely monitored and managed for potential development of CMV reactivation. To this end, periodic monitoring for the presence of CMV antigens using quantitative polymerase chain reaction (PCR) assays is an effective management approach. The panel recommends routine surveillance for CMV viremia (every 2–3 weeks) during the treatment course with alemtuzumab and for 2 months following completion of alemtuzumab treatment.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a rare but serious and usually fatal CNS infection caused by reactivation of the latent JC polyoma virus. Cases of PML generally occur in severely immunocompromised individuals, as in the case of patients with AIDS. Patients with hematologic malignancies who have profound immunosuppression (due to the underlying disease and/or immunosuppressive therapies) are also at risk of developing PML. In a report of 57 cases from the Research on Adverse Drug Events and Reports project, 52 patients with lymphoproliferative disorders developed PML after treatment with rituximab and other treatments which included hematopoietic stem cell transplantation or chemotherapy with purine analogs or alkylating agents. Median time from last rituximab dose to PML diagnosis was 5.5 months. Median time to death after PML diagnosis was 2 months. The case fatality rate
T-cell Lymphomas

was 90%. The use of rituximab may be associated with an increased risk of PML in immunocompromised patients with lymphoproliferative malignancies. PML has been reported with rituximab treatment (usually in combination with chemotherapy regimen) in patients with CLL/SLL or other types of NHL. Patients with low CD4+ T-cells prior to or during anti-tumor treatment with rituximab-containing regimens may be particularly susceptible to PML. Patients with NHL receiving treatment with another anti-CD20 monoclonal antibody ofatumumab, or the anti-CD30 antibody-drug conjugate brentuximab vedotin, may also be at potential risk for PML.

Development of PML is clinically suspected based on neurological signs and symptoms that may include confusion, motor weakness or poor motor coordination, visual changes, and/or speech changes. PML is usually diagnosed with PCR of cerebrospinal fluid (CSF) or in some cases, by analysis of brain biopsy material. There is no effective treatment for PML. Patients should be carefully monitored for the development of any neurological symptoms. There is currently no consensus on pretreatment evaluations that can be undertaken to predict for the subsequent development of PML.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is a potentially serious complication of anticancer therapy characterized by metabolic and electrolyte abnormalities caused by the abrupt release of intracellular contents into the peripheral blood resulting from cellular disintegration induced by anticancer therapy. It is usually observed within 12 to 72 hours after start of chemotherapy. Untreated TLS can induce profound metabolic changes resulting in cardiac arrhythmias, seizures, loss of muscle control, acute renal failure, and even death. Cairo and Bishop have classified TLS into laboratory TLS and clinical TLS. Laboratory TLS is defined as a 25% increase in the levels of serum uric acid, potassium, or phosphorus or a 25% decrease in calcium levels. Clinical TLS refers to laboratory TLS with clinical toxicity that requires intervention. Clinical complications may include renal insufficiency, cardiac arrhythmia, or seizures. The four primary electrolyte abnormalities of TLS are hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia. Symptoms associated with TLS may include nausea and vomiting, diarrhea, seizures, shortness of breath, or cardiac arrhythmias. The risk factors for TLS include bone marrow involvement, bulky tumors that are chemosensitive, rapidly proliferative or aggressive hematologic malignancies, an elevated leukocyte count or pretreatment LDH, pre-existing elevated uric acid, renal disease or renal involvement of tumor. Patients diagnosed with lymphoblastic lymphoma or Burkitt lymphoma are at a higher risk of developing TLS. Occasionally, patients with bulky presentation of DLBCL and patients with CLL and high white blood cell count may experience TLS at a moderately high frequency.

TLS is best managed if anticipated and when treatment is started prior to chemotherapy. The cornerstone of TLS management is hydration and the management of hyperuricemia. Allopurinol (xanthine oxidase inhibitor) and rasburicase (recombinant urate oxidase) are highly effective for the management of hyperuricemia. Allopurinol is a xanthine analog and a competitive inhibitor of xanthine oxidase, thereby blocking conversion of purine metabolites to uric acid. Allopurinol will decrease the formation of uric acid production and has been shown to reduce the incidence of uric-acid uropathy. Since the drug inhibits new uric acid formation rather than reduce existing uric acid, it can take several days for elevated levels of uric acid to normalize after the initiation of treatment, which may delay the start of chemotherapy. Furthermore, allopurinol may lead to the accumulation...
of xanthine crystals in renal tubules leading to acute obstructive uropathy. Allopurinol will also reduce clearance of 6-mercaptopurine and high-dose methotrexate. Rasburicase is a recombinant urate oxidase, which catalyzes the oxidation of uric acid to a highly soluble non-toxic metabolite that is readily excreted. It has been shown to be safe and highly effective in the prevention and treatment of chemotherapy-induced hyperuricemia in both children and adults with hematologic malignancies. In an international compassionate use trial in patients at risk for TLS during chemotherapy (N=280 enrolled), rasburicase (0.20 mg/kg/day IV for 1–7 days) resulted in uric acid response in all evaluable patients (n=219; adults, n=97). Among the subgroup of adults with hyperuricemia (n=27), mean uric acid levels decreased from pretreatment levels of 14.2 mg/dL to 0.5 mg/dL 24 to 48 hours after administration of last dose of rasburicase. Among adult patients at risk for TLS (but without baseline hyperuricemia; n=70), mean uric acid levels decreased from 4.8 mg/dL to 0.4 mg/dL. The GRAAL1 trial evaluated the efficacy and safety of rasburicase (0.20 mg/kg/day IV for 3–7 days, started on day 0 or day 1 of chemotherapy) for the prevention and treatment of hyperuricemia in adult patients with aggressive NHL during induction chemotherapy (N=100). Prior to chemotherapy, 66% of patients had elevated lactate dehydrogenase (LDH) levels and 11% had elevated uric acid levels (>7.56 mg/dL). Uric acid levels were normalized and maintained within normal ranges during chemotherapy in all patients. Uric acid levels decreased within 4 hours after the first injection of rasburicase. In addition, serum creatinine levels and other metabolites were also controlled with the administration of rasburicase.

A prospective, multicenter randomized phase III trial compared the efficacy and safety of rasburicase and allopurinol in adult patients with hematological malignancies at high or potential risk for TLS (N=275). Patients were randomized to receive treatment with rasburicase alone (0.20 mg/kg/day IV for days 1–5; n=92), rasburicase combined with allopurinol (rasburicase 0.20 mg/kg/day IV for days 1–3; allopurinol 300 mg/day PO for days 3–5; n=92) or allopurinol alone (300 mg/day PO for days 1–5; n=91). The rate of uric acid response (defined as plasma uric acid levels ≤7.5 mg/dL for all measurements from days 3–5) was 87% for rasburicase, 78% for rasburicase combined with allopurinol and 66% for allopurinol. The incidence of clinical TLS was similar across treatment arms, occurring in 3%, 3% and 4% of patients, respectively. The incidence of laboratory TLS was 21%, 27%, and 41%, respectively, with significantly lower incidence observed in the rasburicase arm compared with allopurinol (P = .003). The response rate with rasburicase was superior to allopurinol in the overall study population (87% vs. 66%, as above; P = .001) as well as in patients with high risk TLS (89% vs. 68%; P = .001) and in patients with baseline hyperuricemia (90% vs. 53%; P = .015). The median time to control for serum uric acid in hyperuricemic patients was 4 hours for rasburicase, 4 hours for rasburicase combined with allopurinol and 27 hours for allopurinol. Potential hypersensitivity to study regimen was reported in 4% of patients in the rasburicase arm and 1% in the combination arm; no anaphylaxis or grade 4 hypersensitivity reactions were reported in this trial. However, rasburicase can induce anaphylactic reactions. Other adverse reactions include methemoglobinemia and severe hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. A single fixed dose of rasburicase (6 mg) or a single weight-based dose of rasburicase (0.05–0.15 mg/kg) has been shown to be effective in the management of uric acid levels in adult patients with hyperuricemia or with high-risk factors for TLS. A recent phase II randomized trial compared the efficacy of rasburicase administered as a single dose (0.15 mg/kg, followed by additional days of dosing as needed) versus rasburicase (0.15 mg/kg/day) given for 5 days in adult
patients at high risk or potential risk for TLS (N=80 treated). The median pretreatment uric acid level was 8.5 mg/dL for high-risk patients (n=40) and 5.6 mg/dL for potential risk patients (n=40). Nearly all treated patients (99%) showed normalization of uric acid levels within 4 hours after the first dose of rasburicase; levels of uric acid were undetectable (<0.7 mg/dL) in 84% of patients. In the single-dose rasburicase arm, 85% of patients had sustained uric acid response compared with 98% of patients in the 5-day rasburicase arm. Among high-risk patients within the single-dose arm, 6 patients received a second dose of rasburicase to achieve uric acid response.

Allopurinol should be administered prior to the initiation of chemotherapy. Rasburicase is indicated in cases where the uric acid level remains elevated despite treatment with allopurinol or in patients with renal insufficiency. Electrolytes and renal function should be monitored every 6 to 8 hours with appropriate interventions for hyperkalemia and hyperphosphatemia. Careful clinical monitoring will help to preempt complications, and in many cases, admission to ICU may be appropriate. Cardiac monitoring or serial ECG may be beneficial to identify early electrolyte-related cardiac abnormalities. Dialysis may be necessary in cases of anuric acute renal failure.

The NCCN Guidelines recommend allopurinol or rasburicase as first-line and at retreatment of hyperuricemia. Allopurinol be started 2–3 days prior to chemotherapy and continued for 10–14 days. Rasburicase is recommended for patients with any of the following risk factors: presence of any high risk feature (i.e., Burkitt lymphoma or lymphoblastic lymphomas; spontaneous TLS; elevated WBC count; elevated uric acid levels; bone marrow involvement; renal disease or renal involvement by tumor); bulky disease requiring immediate therapy; patients in whom adequate hydration is not possible;
References


Peripheral T-Cell Lymphomas

Peripheral T-cell lymphomas (PTCL) are a heterogeneous group of lymphoproliferative disorder arising from mature T-cells of post-thymic origin. PTCL represent a relatively uncommon group of hematologic malignancies within non-Hodgkin lymphomas (NHL), accounting for about 10% of NHL cases. PTCL—not otherwise specified (PTCL-NOS; 26%) is the most common subtype followed by, angioimmunoblastic T-cell lymphoma (AITL; 18.5%), ALK-positive anaplastic large cell lymphoma (ALCL; 7%), ALK-negative ALCL (6%) and enteropathy-associated T-cell lymphoma (EATL; <5%).

PTCL-NOS most often involves nodal sites, however, many patients present with extranodal involvement including the liver, bone marrow, GI tract and skin. PTCL-NOS is associated with poorer overall survival (OS) and event-free survival (EFS) rates compared to B-cell lymphomas. AITL usually presents with generalized lymphadenopathy, often with associated hypergammaglobulinemia, hepatomegaly or splenomegaly, eosinophilia, skin rash and fever. It occurs mainly in older patients. Prognosis is similar to PTCL-NOS. In a single institution study, which reviewed the data from 199 patients with PTCLs, the 5-year OS and PFS rates were 36% and 13%, respectively, for the subgroup of patients with AITL. In the more recent report from the GELA study, which included the largest series of patients with AITL (n=157), 5- and 7-year OS rates were 33% and 29%, respectively, reaching an apparent plateau around 6 years. The corresponding EFS rates were 29% and 23%, respectively.

ALCL is a CD30-expressing subtype of PTCL which accounts for less than 5% of all cases of NHL. There are now three distinctly recognized subtypes of ALCL: systemic ALK-1 expressing ALCL, systemic ALK-1 negative ALCL, and primary cutaneous ALCL. ALK-positive ALCL is most common in children and young adults and is characterized by the overexpression of anaplastic lymphoma kinase (ALK-1) protein, resulting from a chromosomal translocation [t(2;5)] in 40-60% of patients. The majority of patients with ALCL present with advanced stage III or IV disease (65% for ALK-positive and 58% for ALK-negative) frequently associated with systemic symptoms and extra nodal involvement. In general ALK-positive ALCL is associated with better clinical outcomes than ALK-negative ALCL, PTCL-NOS or AITL, although the favorable prognosis of ALK-1 positivity is diminished with older age and higher prognostic risk scores. In the survival analysis from the International T-cell Lymphoma Project, ALK-positive ALCL was associated with significantly better prognosis with anthracycline-containing regimens compared with ALK-negative ALCL, both in terms of the 5-year failure-free survival (FFS) rate (60% vs. 36%; \( P=0.015 \)) and OS rate (70% vs. 49%; \( P=0.016 \)). The differences in prognosis were most pronounced for younger patients with favorable prognostic factors. The 5-year FFS and OS rates for patients with PTCL-NOS were 20% and 32%, respectively. The 5-year FFS and OS rates for patients with AITL were 18% and 32%, respectively. ALK-negative ALCL was associated with superior survival rates when compared with PTCL-NOS.

Recent molecular and genetic studies have identified distinct subsets of ALK-negative ALCL and PTCL-NOS. In a recent series of 105 patients with ALCL, ALK-negative ALCL with dual-specificity phosphatase 22 (DUSP22) rearrangements by FISH had clinical outcomes similar to that of ALK-positive ALCL. The 5-year OS rates were 85% for ALK-positive ALCL and 90% for ALK-negative ALCL with DUSP22 rearrangement. In another series of 372 patients with PTCL,
gene expression profiling (GEP) identified 2 major molecular subgroups of PTCL-NOS, characterized by high expression of either GATA3 or TBX21. High expression of GATA3 was significantly associated with poor overall survival.\textsuperscript{12}

EATL is a rare T-cell lymphoma of the small intestine, accounting for <1% of all the NHLs and associated with a very poor prognosis. The median age of diagnosis is 60 years. The typical immunophenotype of EATL is CD3+, CD5–, CD7+, CD8–/+, CD4– and CD103+. Anthracycline-based chemotherapy with CHOP or CHOP-like regimens is most commonly used for patients with EATL.\textsuperscript{13-16} However, outcomes remain poor with these conventional therapeutic approaches. In the aforementioned analysis from the International T-cell Lymphoma Project, the 5-year FFS and OS rates in patients with EATL primarily treated with anthracycline-based regimens were 4% and 20%, respectively.\textsuperscript{3}

Primary cutaneous variant of ALCL is noted for the absence of ALK1 protein and for an indolent disease course characterized by frequent relapses, generally confined to the skin. Primary cutaneous ALCL is associated with long-term survival despite cutaneous relapses. As a result, combination chemotherapy is rarely indicated for these patients. In the aforementioned analysis conducted by the International T-cell Lymphoma Project, the 5-year FFS and OS rates among patients with primary cutaneous ALCL were 55% and 90%, respectively.\textsuperscript{3}

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines\textsuperscript{®} for Non-Hodgkin’s Lymphomas an electronic search of the PubMed database was performed to obtain key literature in “Peripheral T-cell lymphomas” published between June 2014 and February 2016 using the following search terms: peripheral T-cell lymphoma, anaplastic large cell lymphoma, angioimmunoblastic T-cell lymphoma and enteropathy-associated T-cell lymphoma. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.\textsuperscript{11}

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 118 citations and their potential relevance was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN webpage.

Staging and Prognosis

Staging is similar to that of the other aggressive lymphomas. However, the prognosis for PTCL remains poor in comparison to B-cell NHL largely due to lower response rates and less durable responses to standard combination chemotherapy regimens such as CHOP. Progress has been further hampered by the relative rarity and the biological heterogeneity.
Historically, the International Prognostic Index (IPI) derived for DLBCLs has been used and was shown to have prognostic value for patients with PTCL.\(^4,8,17\) In an analysis of 340 patients with PTCL-NOS included in the International T cell Lymphoma Project, IPI was predictive of both OS and PFS (\(P < .001\)).\(^8\) In a retrospective study that analyzed the initial characteristics and prognostic features in 174 patients diagnosed with PTCL, the histologic subgroup (ALCL vs. other PTCL), the presence of B-symptoms and the IPI (low vs. high) maintained independent predictive value in multivariate analysis.\(^17\) The complete response (CR) rates (69% vs. 45%) and median survival (65 months vs. 20 months) were better for ALCL subgroup compared to other PTCL subtypes. A retrospective GELA study compared the prognosis of patients with PTCL (including all subgroups) with the prognosis of B-cell lymphoma patients with similar characteristics receiving similar aggressive combination chemotherapy, and in some patients, receiving HDT/ASCR.\(^4\) The CR rates (63% vs. 54%), 5-year event-free survival (EFS) rates (45% vs. 32%) and 5-year OS rates (52% vs. 41%) were higher for patients with B-cell lymphomas compared with patients with PTCL. The difference in 5-year OS rates between B-cell lymphomas and PTCL were most pronounced in patients with 2 or 3 adverse risk factors as determined by IPI (53% vs. 36% for 2 risk factors; and 35% vs. 23% for 3 risk factors).\(^4\) A more recent analysis also demonstrated that the 3-year PFS and OS rates for patients with newly diagnosed PTCL (32% and 52%, respectively) were significantly inferior to the matched cohort of patients with DLBCL and there was no clear benefit for patients undergoing consolidative SCT.\(^18\) Stage I-II disease was the only significant pretreatment prognostic factor in the multivariate analysis. ALK-positivity was a prognostic factor on univariate analysis, but lost its significance on multivariate analysis.\(^18\)

In 2004, the Italian Intergroup for lymphoma proposed a new prognostic index for PTCL-NOS, known as the Prognostic Index for PTCL-U (PIT).\(^19\) Risk factors identified based on multivariate analysis included the following: age older than 60 years, elevated LDH levels, performance status of 2 or more, and bone marrow involvement. Five-year OS rate was only 33% for patients with 2 risk factors and 18% for those with 3 or 4 risk factors. This schema also identified a subset of patients with relatively favorable prognosis, who had adverse risk factors.\(^19\) This group represented 20% of patients and had a 5-year OS rate of 62%.

Both IPI and PIT can be used to stratify for prognosis and under certain circumstances may aid in guiding treatment decisions for patients with PTCL.

**Diagnosis**

Diagnosis of PTCL is similar to that described for other lymphomas, requiring adequate immunophenotyping to distinguish PTCL from B-cell neoplasms. The initial paraffin panel for immunohistochemistry (IHC) studies may only include pan-T-cell markers and can be expanded to include antibodies of T-cell lymphoma, if suspected. The following markers should be considered for the IHC analysis: CD2, CD3, CD5, CD7, CD4, CD8, CD30, CD56, CD57, CD10, CD20, CD21, CD23, ALK, EBER-ISH, BCL6, and Ki-67. Alternatively, the following markers can be analyzed by flow cytometry: CD2, CD3, CD5, CD7, CD4, CD8, CD30, CD10, CD19, CD20, CD45, kappa/lambda, TCR\(\alpha\beta\), and TCR\(\gamma\). Additional IHC studies to evaluate \(\beta\)F1, CD279/PD1, and CXCL-13 may be useful under certain cases to establish lymphoma subtype. PTCL is often associated with clonal rearrangements of the T-cell receptor (TCR) genes that are less frequently seen in non-cancer T-cell diseases, although false positive results or non-malignant clones can at
times be identified. Under certain circumstances, molecular analysis to detect TCR gene rearrangements and translocations involving the ALK gene, i.e., t(2;5) or variant, may be useful.

PTCL-NOS has variable T-cell associated antigens and usually lacks B-cell associated antigens (although aberrant CD20 expression in T-cell lymphomas is infrequently encountered). With the exception of CD30 expression in ALCL, antigen expression is variable across the aggressive T-cell lymphomas. The majority of the nodal cases express CD4+ and lack CD8-, however CD4-/CD8+, CD4+/CD8-, and CD4+/CD8+ cases are seen.20 While CD30 expression can be found at times in many T-cell lymphomas, systemic ALCL has uniform strong expression of CD30. In ALCL cases only, evaluation of ALK1 status, either based on immunophenotyping or genetic analysis of the t(2;5) or variant chromosomal rearrangements, is important to identify the ALK1 positive tumors that have a better prognosis. AITL cells express T-cell associated antigens and are usually CD4+. Expression of CXCL13 has been identified as a useful marker that may help distinguish AITL from PTCL-NOS.21,22 It is also characterized by the frequent presence of Epstein-Barr virus (EBV)-positive B-cells and cases of co-existent EBV+DLBCL are reported. EBER (EBV-encoded RNA) is positive in about 40% of PTCL and some case series have reported that EBER positive tumors have a worse prognosis.

Workup
The workup for PTCL is similar to the workup for other lymphoid neoplasms, focusing on the determination of stage, routine laboratory studies (CBC with differential and platelets, comprehensive metabolic panel), and physical examination including a full skin exam, and imaging studies, as indicated. CT scan with diagnostic quality and/or PET-CT scan of the chest, abdomen, and pelvis are essential during workup. In some cases, CT scan of the neck and CT or MRI of the head may be useful. MUGA scan or echocardiogram is also recommended, since chemotherapy is usually anthracycline based. In selected cases, serology testing for HIV and HTLV-1 (human T-cell lymphoma virus) may be useful. HTLV-1 positivity, in particular, can lead to the alternate diagnosis and alternate management of ATLL for cases that would otherwise be classified as PTCL-NOS by the pathologist if positive HTLV-1 serology was not known.

Induction Therapy
PTCLs are less responsive to and have less frequent durable remissions with standard chemotherapy regimens such as CHOP and thus carry a poorer prognosis compared to diffuse large B-cell lymphomas. In prospective randomized studies, PTCLs have been included with aggressive B-cell lymphomas.23,24 However, it has not been possible to assess the impact of chemotherapy in this subgroup of patients with PTCL due to small sample size. Only limited data exist from randomized trials comparing the efficacy of chemotherapy regimens exclusively in patients with PTCL.25

CHOP chemotherapy is the most commonly used first-line regimen for patients with PTCL. However, with the exception of ALK+ ALCL, outcomes are disappointing in patients with the most common forms of PTCLs, namely PTCL-NOS and AITL compared to the favorable results achieved with DLBCL.10 In a retrospective study conducted by the British Columbia cancer agency, the 5-year OS rate for patients with PTCL-NOS primarily treated with CHOP or CHOP-like regimens was only 35%; among these patients, the 5-year OS rates were higher in patients with low-risk IPI scores compared with those with high-risk IPI scores (64% vs. 22%, respectively).5 In addition, patients with
ALK-positive ALCL had superior clinical outcome compared to those with ALK-negative ALCL (5-year OS 58% vs. 34%, respectively).

Chemotherapy regimens that are more intensive than CHOP have not shown any significant improvement in OS in patients with PTCL, with the exception of ALCL. In a randomized study by the German High-grade NHL Study Group (DSHNHL), the addition of etoposide to CHOP (CHOEP regimen), the addition of etoposide to CHOP (CHOEP regimen) resulted in significantly higher CR rate (88% vs. 79% for CHOP; \( P = 0.003 \)) and 5-year EFS rate (69% vs. 56% for CHOP; \( P = 0.004 \)) with no difference in OS outcomes between the regimens. It should also be noted that in this study, the majority of patients had aggressive B-cell NHL and were relatively young with favorable prognosis (age \( \leq 60 \) years; normal LDH levels), with only 14% diagnosed with T-cell NHL (ALK, 9.4%; PTCL-NOS, 2.5% and AITL, 0.1%). In an analysis of a large cohort of patients with PTCL treated within the DSHNHL trials, patients with ALK-positive ALCL had favorable outcomes with CHOP or CHOP with etoposide (CHOEP). Three-year EFS and OS rates were 76% and 90%, respectively, for patients with ALK-positive ALCL. The corresponding outcomes were 50% and 67.5%, respectively, for AITL, 46% and 62%, respectively, for ALK-negative ALCL and 41% and 54%, respectively, for PTCL-NOS. CHOEP was associated with a trend for improved EFS among relatively young patients (age \( <60 \) years) and is an option for these patients. CHOP-21 appeared to be the standard regimen for patients age \( >60 \) years, given that the addition of etoposide did not provide an advantage in these older patients due to increased toxicity. Among patients with ALK-negative ALCL, AITL and PTCL-NOS, those with low-risk IPI scores (IPI <1) had a relatively favorable prognosis; conversely, patients with higher risk IPI scores had low rates of EFS and OS with CHOP or CHOEP. In a retrospective analysis of data from patients with T-cell malignancies treated at the MD Anderson Cancer Center (N=135; PTCL-NOS, n=50; ALCL, n=40; AITL, n=14), CHOP was compared with more intensive chemotherapy regimens, one of which included a regimen with hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and prednisone (hyper-CVAD). The estimated median OS was 46 months for all patients. The 3-year OS rate with CHOP and intensive therapies was 62% and 56%, respectively. Within the subgroup of patients with ALCL, those with ALK-positive disease showed a trend for a higher 3-year OS rate compared with those with ALK-negative ALCL (100% vs. 70%, respectively). When the subgroup with ALCL was excluded from the analysis, the median OS was 21 months; the 3-year OS rate with CHOP and intensive therapies was 43% and 49%, respectively.

In a prospective study, dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin) was associated with favorable outcome in previously untreated patients with ALCL (n =24; ALK-positive ALCL, n=15; ALK-negative ALCL, n=9). At a median follow-up 14 years, the EFS rates were 72% and 62.5% \( (P = 0.54) \), respectively for patients with ALK-positive ALCL and ALK-negative ALCL and the OS rates were 78.0% and 87.5%, respectively \( (P = 0.83) \), respectively. However, definitive conclusions from these findings are limited by the small number of patients and possible selection bias (24 patients recruited over 16 years and the median age patient was 36 years for the ALK-positive ALCL and 43 years for ALK-negative ALCL).

First-line Consolidation Therapy with HDT/ASCR
The generally poor results with conventional chemotherapy have led many to explore the role of HDT/ASCR as a first-line consolidation therapy option. Several retrospective studies have reported favorable outcomes in patients with PTCL undergoing HDT/ASCT during first-line or subsequent lines of therapy; the 3-year OS rate ranged from 53% to
58%; the 3-year PFS rate correlated with OS outcomes, and ranged from 44% to 50%.30-36

HDT/ASCR as first-line consolidation therapy for patients with PTCL has also been evaluated in prospective studies.37-41 The pooled results from two prospective studies (N=62) showed that at a median follow-up of 76 months, the estimated 12-year OS and EFS rates were 34 and 30%, respectively, for the whole study cohort.37 The 10-year OS and EFS rates were significantly higher among the patients with ALK-positive ALCL (63% and 54%, respectively) compared with patients with other PTCL subtypes (21% and 19%, respectively). In the subgroup of patients with PTCL-NOS, the corresponding survival rates were 37% and 25%, respectively.37 Overall treatment-related mortality rate was 5%. In a multivariate analysis, the achievement of CR before transplant was a strong predictor of survival benefit. The projected 10-year OS and EFS rates for patients in CR before transplant were 48% and 47%, respectively, compared with 22% and 11%, respectively, for those who were not in CR prior to transplant.37 In the prospective study conducted by the GELTAMO Study group (N=26), patients with CR or PR to induction therapy with MegaCHOP were planned for ASCR.38 The 3-year OS and PFS rates on an intent-to-treat basis were 73% and 53%, respectively. At 2-year post-transplant follow-up, OS and PFS rates were 84% and 56%, respectively, among the patients who proceeded to ASCR consolidation (n=19). In a phase II study (n=41), high-dose CHOP regimen alternating with etoposide, cisplatin, cytarabine and prednisone followed by ASCT, resulted in a CR rate 51%. With a median follow-up of 3.2 years, the 4-year OS and PFS rates were 39% and 30%, respectively.39

Reimer et al reported the final analysis of the first prospective PTCL-restricted multicenter study on upfront HDT/ASCR in 83 patients.40 The treatment regimen consisted of four to six cycles of CHOP followed by HDT/ASCR. The ORR following CHOP chemotherapy was 79% (39% CR). Fifty-five of the 83 patients (66%) received transplantation; the remaining 34% of patients were unable to proceed to transplant, primarily due to progressive disease. After HDT/ASCR, 48 of the 55 patients achieved a CR, and 7 patients achieved a PR. In an intent-to-treat analysis, the ORR after myeloablative therapy was 66% (56% CR). The estimated 3-year OS and PFS rates were 48% and 36%, respectively.

In the largest prospective trial of HDT/ASCR as part of initial therapy in PTCL, the Nordic lymphoma group evaluated dose-dense induction therapy with CHOEP followed by HDT/ASCR in patients with previously untreated PTCL (NLG-T-01 study).41 Patients with ALK-positive ALCL were excluded from this study. Among 160 patients enrolled with histopathologically confirmed PTCL (PTCL-NOS, 39%; ALK-negative ALCL, 19%; AITL, 19%; EATL, 13%) who had achieved CR/PR to induction therapy, 115 patients (72%) underwent HDT/ASCR.41 In intent to treat analysis, at a median follow-up of 60.5 months, the 5-year OS and PFS rates were 51% and 44%, respectively. Treatment-related mortality (TRM) was 4%. Patients with ALK-negative ALCL had the highest 5-year OS and PFS survival rates (70% and 61%, respectively).41 The 5-year OS and PFS rates were 47% and 38%, respectively, for the subgroup of patients with PTCL-NOS; 52% and 49% respectively, for patients with AITL and 48% and 38%, respectively for patients with EATL. Long-term follow-up results also confirmed the efficacy of CHOEP followed by HDT/ASCR as an upfront treatment for patients with previously untreated PTCL.42 At a median follow-up of 10 years, the 10-year OS and PFS rates for the whole intent-to-treat population were 41% and 38% respectively. The 10-year OS and PFS rates were both 48% for patients with ALK-negative ALCL and the
survival rates for patients with PTCL-NOS, AITL and EATL did not differ substantially from the 5-year follow-up analysis.\textsuperscript{42} In a more recent phase II study, CHOP plus alemtuzumab followed by HDT with autologous or allogeneic HSCT as initial therapy effectively prolonged DFS in younger patients with PTCL (≤ 60 years old).\textsuperscript{43} At a median follow-up of 40 months, the 4-year OS, PFS, DFS rates were 49%, 44% and 65%, respectively. At a median follow-up of 48 months, the corresponding survival rates for older patients were 31%, 26% and 44%, respectively after initial therapy with CHOP plus alemtuzumab. An ongoing international randomized phase III trial is evaluating the role of adding the alemtuzumab to CHOP (versus CHOP alone; standard arm) in patients with previously untreated PTCL (ACT-1, younger patients 18–60 years; ACT-2, patients >60 years).\textsuperscript{44,45} Patients with ALCL were excluded regardless of ALK status. In the ACT-1 trial, patients ≤ 60 years were eligible to proceed with HDT/ASCR. Results from the planned interim analysis of the ACT-1 trial (n=68) reported 1-year overall non-arm specific EFS of 55%.\textsuperscript{44} The corresponding 1-year OS and PFS rates were 78% and 54%, respectively. Viral infectious events were more frequent in the alemtuzumab arm (28% vs. 10%), primarily due to asymptomatic cytomegalovirus (CMV) reactivations. The frequency of grade 3 or higher bacterial and fungal infections were similar between treatment arms. The final analysis of the ACT-2 trial (n = 116) showed that the addition of alemtuzumab to CHOP resulted in increased CR rates (60% vs. 43% for CHOP) but there was no improvement in PFS and OS rates mostly due to treatment related toxicity.\textsuperscript{45} The 3-year PFS and OS rates were 26% and 38% respectively for CHOP + alemtuzumab compared to 29% and 56% for CHOP. The Hematotoxicity grade 3 or 4 hematologic toxicities (70% vs. 54%) and grade ≥ 3 infections were more frequent with CHOP + alemtuzumab A-CHOP (40 vs. 21%).

HDT/ASCR may offer a feasible option for patients with AITL, particularly in the setting of first remission.\textsuperscript{46-48} In an analysis of data from a large cohort of patients with AITL from the EBMT Lymphoma Registry (N=146), the 2-year and 4-year OS rates overall for patients undergoing HDT/ASCR were 67% and 59%, respectively.\textsuperscript{47} For the subgroup of patients who underwent HDT/ASCR in first CR, the 2-year and 4-year OS rates were 81% and 78%, respectively. Recent studies have shown that more intensive regimens followed by high-dose therapy followed by autologous stem cell rescue (HDT/ASCR) may improve outcomes in patients with EATL.\textsuperscript{49-52} CHOP followed by IVE (ifosfamide, etoposide and epirubicin) alternating with intermediate-dose methotrexate) and HDT/ASCR as initial therapy significantly improved outcomes in patients with EATL.\textsuperscript{50} The 5-year PFS and OS rates were 52% and 60% respectively, which were significantly higher in historical comparison with the corresponding survival rates reported with conventional anthracycline-based chemotherapy (the 5-year PFS and OS rates were 22%). In an intention-to-treat analysis of 252 patients with nodal PTCL (excluding ALK-positive ALCL) and EATL from the Swedish Lymphoma Registry, CHOEP followed by upfront consolidation with HDT/ASCR resulted in superior OS (HR, 0.58; P = .004) and PFS (HR, 0.56; P = .002) rates compared to those treated without HDT/ASCR.\textsuperscript{51}

Longer follow-up and preferably a randomized trial, is necessary to evaluate the impact of first-line consolidation therapy on time-to-treatment failure and OS outcomes. In the absence of randomized trials comparing conventional chemotherapy to first-line consolidation with HDT/ASCR, this is a reasonable treatment option only in patients showing good response to induction therapy.
NCCN Recommendations

Multiagent chemotherapy (CHOP-21 or CHOEP) for 6 cycles with or without ISRT (30-40 Gy) or for 3-4 cycles with ISRT (30-40 Gy) is considered as the standard first-line therapy for patients with stage I, II ALK-positive ALCL. Multiagent chemotherapy alone (CHOP-21 or CHOEP) for 6 cycles is recommended for patients with stage III-IV ALK-positive ALCL.

Although CHOP or CHOEP regimens are associated with a favorable prognosis in patients with ALK-positive ALCL, these regimens have not resulted in similarly favorable outcomes for patients with other PTCL histologies. Thus, participation in clinical trials is the preferred management approach for patients with other subtypes (PTCL, NOS, ALK-negative ALCL, AITL and EATL). In the absence of suitable clinical trials, multiagent chemotherapy (6 cycles) with or without ISRT (30-40 Gy) is recommended for all patients (stage I-IV disease). Suggested multiagent chemotherapy regimens include CHOEP, CHOP-14, CHOP-21, dose-adjusted EPOCH CHOP followed by IVE alternating with intermediate-dose methotrexate (evaluated only in patients with EATL), or hyper-CVAD.

AITL is a highly heterogeneous disease and in selected situations at times may be treated solely with corticosteroids or other immunosuppressive agents. Most patients with AITL are managed similarly to other forms of PTCL as above; however the NCCN Guidelines panel suggests a trial of singe-agent corticosteroid for symptom management in elderly patients or in patients with comorbid conditions in whom the risks of combination chemotherapy are excessive.

Results from recent studies that have evaluated the utility of PET scans for assessment of response to therapy suggest that a positive PET scan after first-line therapy or second-line therapy for relapsed/refractory disease is predictive of worse outcomes and the use of interim PET scans may be helpful in determining the prognosis and refine response assessments. However, the optimal use of PET scans for the evaluation of response to treatment has not yet been established.

The guidelines recommend interim restaging after completion of initial therapy for all patients (except for those with ALK-positive ALCL). If a PET-CT scan is positive, re-biopsy is recommended before changing course of treatment. Patients are then divided into three groups according to treatment response (CR, PR or no response or progressive disease). Patients with a CR can be either be observed or treated with consolidative HDT/ASCR. Local RT can be given prior to or following HDT. Patients with PR or no response or progressive disease after initial therapy are treated similarly to patients with relapsed or refractory disease.

Treatment for Relapsed or Refractory Disease

Role of Transplant

HDT/ASCR in patients with relapsed or refractory PTCL-NOS been evaluated in several retrospective studies. In a retrospective analysis of data from the Spanish Group for Lymphoma and Autologous Transplantation (GEL-TAMO) registry (n=115), the 5-year OS rate was 45% for the group of patients with PTCL treated with HDT/ASCR in the second-line setting (n=78) compared with 80% for those who were transplanted in first CR (n=37) (P=0.007). Within the group of patients in the second-line setting, the 5-year OS rates for patients who underwent HDT/ASCR in first PR, CR at second-line or later lines of therapy, or with refractory disease, were 46%, 54%, and 0%, respectively. In a retrospective analysis of patients with relapsed or primary refractory PTCL (n=36) undergoing HDT/ASCR, the 3-year OS and EFS rates were 48% and 37% respectively, which in retrospective...
comparison appeared similar to the outcomes of patients with relapsed diffuse large B-cell lymphoma (DLBCL) who received HDT/ASCR (53% and 42%, respectively). In another retrospective study of patients with relapsed or primary refractory PTCL (n=24; excluding patients with ALK-positive ALCL) who received HDT/ASCR after responding to second-line therapy, the 5-year PFS and OS rates were 24% and 33%, respectively; these outcomes also appeared similar to outcomes in patients with relapsed DLBCL (34% and 39%, respectively). In another retrospective review of patients with PTCL who underwent HDT/ASCR at Stanford University (n=53), the disease status and the number of regimens received prior to transplant were significant prognostic factors. The 5-year PFS rates for patients in first CR/PR, CR/PR after second-line therapy and those with refractory disease were 51%, 12%, and 0%, respectively; the 5-year OS rates were 76%, 40%, and 30%, respectively.

Nevertheless, second-line therapy for patients with relapsed/refractory PTCL remains suboptimal, even with the incorporation of HDT/ASCR. While HDT/ASCR has been reported to result in survival rates comparable to DLBCL in patients with relapsed/refractory PTCL, it remains a significant challenge, especially for patients with ALCL. Recent reports have shown that allogeneic SCT using myeloablative conditioning or reduced intensity conditioning (RIC) may provide an option for patients with relapsed or refractory PTCL. In a phase II study, Corradini et al investigated the role of RIC allogeneic SCT in patients with relapsed or refractory PTCL (n=17). The estimated 3-year PFS and OS rates were 64% and 81%, respectively. Donor lymphocyte infusion induced responses in some patients progressing after allografting. The estimated probability of non-relapse mortality (NRM) at 2 years was 6%. In a retrospective analysis of data from the French registry for patients who received allogeneic SCT with myeloablative conditioning (N=77; PTCL-NOS 35%; ALCL 35%; AITL 14%), the 5-year EFS and OS rates were 53% and 57%, respectively. The 5-year transplant-related mortality (TRM) rate was 34%; TRM at 100 days was 21%. Patients who received ≤2 lines of prior chemotherapy had significantly higher 5-year OS rate compared with those who received >2 lines (73% vs. 39%; P=0.003). The 5-year OS rate was also significantly higher among patients transplanted in remission (CR or PR) compared with those who were transplanted with less than a PR (69% vs. 29%; P=0.0003). No significant differences in outcomes (OS, EFS, or TRM) were observed between types of conditioning regimen. Based on multivariate analysis, resistant disease (less than PR) at the time of transplantation and severe acute graft-versus-host disease (GVHD) were significant independent predictors for worse survival outcomes. A retrospective study of data from the EBMT database demonstrated that allogeneic SCT induced long-term remissions in patients with AITL (N=45; 62% of patients had ≥2 lines of therapy prior to transplantation). Myeloablative conditioning was employed in 56% of patients while the remaining patients received RIC. The cumulative NRM rate at 1 year was 25%; these rates were similar between myeloablative conditioning (29%) and RIC (24%). The estimated 3-year relapse rate was 20%. The 3-year PFS and OS rates were 54% and 64%, respectively. These outcomes were not significantly different between conditioning regimens. Patients with chemotherapy-sensitive disease had a significantly higher rate PFS compared with those with refractory disease (66% vs. 33%, respectively). A retrospective analysis of long-term data from patients...
with relapsed/refractory PTCL treated with RIC allogeneic SCT (N=52; PTCL-NOS, n=23; ALCL, n=11; AITL, n=9) showed 5-year PFS and OS rates of 40% and 50%, respectively. The 5-year NRM rate was 12%, and extensive chronic GVHD was associated with increased risks for NRM. The 5-year cumulative relapse rate was 49%; worse disease status at the time of transplantation and greater lines of prior therapy were associated with higher relapse risks. Further prospective data are needed to determine the role of allogeneic SCT (either with myeloablative conditioning or RIC) in patients with relapsed/refractory PTCL.

In an analysis of data from CIBMTR that evaluated outcomes with HDT/ASCR and allogeneic stem cell transplantation (SCT) in patients with T-cell lymphomas (n=241; 112 patients with ALCL; 102 patients with PTCL and 27 patients with AITL), HDT/ASCR resulted in improved outcomes compared with allogeneic SCT for the subgroup of patients with ALCL but not for other subtypes. Among patients with ALCL (n=111), HDT/ASCR resulted in significantly higher 3-year PFS (55% vs. 35%; P=0.03) and OS (68% vs. 41%; P=0.003) with significantly reduced NRM and overall mortality compared with allogeneic SCT. Survival outcomes with HDT/ASCT appeared less favorable for patients with PTCL-NOS (n=102), and no significant differences in outcomes were observed between HDT/ASCR and allogeneic SCT with regards to 3-year PFS (29% vs. 33%) or OS (45% vs. 42%) in this subgroup. The overall non-relapse mortality rate for all patients at 100 days was 2% for the HDT/ASCR group compared with 19% for the myeloablative allogeneic SCT group and 18% for the reduced-intensity conditioning allogeneic SCT. A higher percentage of patients undergoing HDT/ASCR had ALCL histology, chemosensitive disease, and were transplanted in first CR. Allogeneic SCT recipients had more bone marrow involvement, more lines of chemotherapy prior to transplant, extranodal disease at diagnosis and higher second-line prognostic index at transplantation. For the group of patients who were transplanted in the salvage setting (i.e., less than first CR), the corresponding 3-year OS rates were 53%, 31% and 50% respectively. For patients who received transplantation beyond first CR, HDT/ASCR resulted in numerically higher 3-year PFS (41% vs. 33%) and OS (53% vs. 41%) compared with allogeneic SCT, but these differences were not statistically significant; cumulative incidence of non-relapse mortality was higher with allogeneic SCT compared with HDT/ASCR in patients transplanted beyond first CR (P<0.001).

In a recent analysis of single-institution data from the M.D. Anderson Cancer Center, outcomes were reported for 134 patients with T-cell lymphomas who underwent HDT/ASCR and allogeneic SCT either as frontline consolidation (n = 58) or for relapsed disease (n = 76). PTCL-NOS and AITL were the dominant histological types. Among patients who were underwent HDT/ASCR (n=41) or allogeneic SCT (n = 35) for relapsed disease, the 4-year OS rates for HDT/ASCR and allogeneic SCT were 50% and 36%, respectively (P < .05). The 4-year PFS rates were not statistically significantly different between the 2 groups (38% and 28%). The 4-year OS rates were of 59% and 53%, respectively for patients with who were in CR2 and CR3 at the time of transplant. The corresponding survival rates for those who were in PR were 55% and 22%, respectively. Patients with chemorefractory disease had inferior outcomes than those with chemosensitive disease, however, the results were not significantly different between HDT/ASCR and allogeneic SCT. The 4-year OS rates were 29% and 35%, respectively (P =6) and the 4-year PFS rates 25% and 18%, respectively (P = .4). The 4-year non-relapse mortality rate was significantly higher with allogeneic SCT (40% vs.17% for HDT/ASCR; P < .001).
Thus, these findings suggest that HDT/ASCR less frequently results in durable benefit in patients with relapsed or refractory disease as compared to allogeneic SCT. However, this conclusion is not universal in the literature and those with relapsed ALCL and more chemosensitive relapsed disease appear to benefit from HDT/ASCR more often those with non-ALCL subtypes and less chemosensitive disease. Allogeneic stem cell transplant SCT using reduced intensity conditioning (RIC) may provide a more reliably curative option for the majority of patients with relapsed or refractory PTCL, based on the patient’s eligibility for transplant.62-65

**Second-line Systemic Therapy**

Until recently, data to guide the treatment of relapsed and refractory PTCL with various single agents (such as alemtuzumab, bortezomib, gemcitabine and lenalidomide) came from small single institution series. In a pilot study, alemtuzumab at standard dose schedule produced an ORR of 36% (CR 21%) among patients with relapsed or chemotherapy-refractory PTCLs (n=14).68 However, alemtuzumab was associated with significant hematologic toxicity and infectious complications, including 5 deaths due to opportunistic infections.68 The preliminary results of another phase II study showed that in patients with pretreated T-cell lymphoma (n =10; PTCL, n=6), alemtuzumab at a reduced dose was less toxic and as equally effective as the standard dose used in the prior pilot study.69 In the subset of patients with PTCL-NOS, ORR was 50% (CR 33%). The median duration of response was 7 months. CMV reactivation was observed only in 10% of patients, as compared with 42% of the patients reported by Enblad et al.68

Long-term follow-up data from a small series of 39 patients with pretreated relapsed/refractory T-cell lymphoma showed that single agent gemcitabine resulted in an ORR of 55% (CR 30%) in a subgroup of 20 patients with PTCL-NOS, 5 of these patients were in continuous CR with a median response duration of 34 months (range, 15-60 months).70 Bortezomib also has demonstrated activity in patients with relapsed or refractory cutaneous T-cell lymphoma (10 patients with MF and 2 patients with PTCL-NOS with isolated skin involvement), resulting in an ORR of 67% (17% CR and 50% PR).71 Histologically, responses were observed in 7 patients with CTCL and one patient with PTCL-NOS with isolated skin involvement. All responses were durable, lasting from 7 to 14 or more months.

Lenalidomide monotherapy has also been effective in the treatment of relapsed or refractory PTCL resulting in an ORR of 24%. The median OS and PFS were 12 months and 4 months respectively, with median duration of response of 5 months.72 The results of a multicenter, single-arm, phase II trial (EXPECT) that evaluated the efficacy of lenalidomide monotherapy in patients with relapsed or refractory PTCL (n = 54), showed that lenalidomide was particularly active in patients with relapsed or refractory AITL. The ORR was 22% (11% CR or CRu) for the entire study population.73 The median PFS and median duration of response were 2.5 months and 3.6 months, respectively, in the intent-to-treat population. Among patients with AITL, the ORR, median PFS and median duration of response were 31% (15% CR/CRu), 4.6 months and 3.5 months, respectively.

Cyclosporine has also been reported as treatment option for patients with relapsed AITL.74 In a small series of 12 patients with relapsed/refractory AITL that had failed prior therapy with steroid or multiagent chemotherapy, cyclosporine, at fairly high doses, induced complete and partial responses in 3 and 5 patients respectively.74 A more recent case report also demonstrated that cyclosporine is an effective treatment for AITL relapsing after HDT/ASCR.75
Pralatrexate is a new antifolate with a high affinity for reduced folate carrier type 1 (RFC-1), and has shown significant activity in patients with relapsed/refractory T-cell lymphoma. The pivotal, international, phase II study (PROPEL) evaluated pralatrexate in heavily pretreated patients with relapsed or refractory PTCL (n = 109; 59 patients with PTCL-NOS; 13 patients with AITL and 17 patients with ALCL). Patients on this study had received a median of 3 prior systemic therapies; 63% were refractory to their most recent prior therapy, 24% had never responded to any prior therapy, and 16% had received prior autologous SCT. Pralatrexate resulted in an ORR of 29% (CR 11%; see independent central review). While the study was not statistically designed to analyze the ORR in specific subsets, response analyses by key subsets indicated that the ORR was lower in AITL (8%) than in other 2 subtypes (32% and 35% respectively for PTCL-NOS and ALCL). The median duration of response was 10 months. For all patients, the median PFS and OS were 3.5 months and 14.5 months, respectively. The most common grade 3-4 adverse events included thrombocytopenia (32%), neutropenia (22%), anemia (18%), and mucositis (22%). In September 2009, pralatrexate became the first FDA-approved single agent for the treatment of patients with relapsed or refractory PTCL.

Bendamustine was evaluated in a multicenter phase II study (BENTLEY trial) in patients with relapsed or refractory PTCL (n=60; AITL, 53%; PTCL-NOS, 38%). Patients had received a median of 1 prior therapy (range, 1–3) and 45% were considered refractory to their last therapy; 92% had received prior CHOP or CHOP-like regimens. Forty patients (67%) had completed 3 or more cycles of bendamustine; 25% received all 6 cycles of therapy. The ORR after 3 cycles of bendamustine was 50% with CR (including CRu) in 28% of patients. The median duration of response was short, at only 3.5 months. The ORR for AITL and PTCL-NOS was 69% and 41%, respectively (P = .47). However, this study was not powered to show differences in response rates between the different histologic subtypes. The median PFS and OS for all patients were 3.6 months and 6.3 months, respectively. The most common grade 3 or 4 toxicity included neutropenia (30%), thrombocytopenia (24%), and infectious events (20%).

Histone deacetylase (HDAC) inhibitors including romidepsin and belinostat have shown single-agent activity in patients with relapsed or refractory PTCL. Romidepsin was approved by the FDA in June 2011 for the treatment of patients with relapsed PTCL based on the results of the pivotal multicenter phase II study that evaluated romidepsin in 130 patients with relapsed/refractory PTCL (PTCL-NOS, n=69 [53%]; AITL, n = 27 [21%]; ALK-negative ALCL, n = 21 [16%]). Patients had received a median of 2 prior systemic therapies (range, 1–8), and 16% had failed prior autologous HSCT. Updated results from this study confirmed that responses were durable across all 3 subtypes of PTCL. At a median follow-up of 22.3 months there were no significant differences in ORR or rates of CR/CRu between the 3 most common subtypes of PTCL. The ORR was 29%, 30% and 24% respectively for patients with PTCL-NOS, AITL and ALK-negative ALCL. The corresponding rates of CR/CRu were 14%, 19% and 19% respectively. The median PFS was 20 months for all responders and it was significantly longer for patients who achieved CR/CRu for ≥12 months than those who achieved CR/CRu for < 12 months or PR (29 months, 13 months and 7 months respectively). The median OS was not reached for patients who achieved CR/CRu and 18 months for those who were in PR. The most common grade ≥3 adverse events included thrombocytopenia (24%), neutropenia (20%), and infections (19% for any; including pneumonia [5%] and sepsis [5%]). The BELIEF trial evaluated belinostat in 129 patients with relapsed or refractory PTCL.
refractory PTCL (pretreated with more than one prior systemic therapy). The ORR in 120 evaluable patients was 25.8% (CR rate of 10.8% and PR rate of 15%). The median duration of response, median PFS and median OS were 13.6 months, 1.6 months and 7.9 months respectively. The 1-year PFS rate was 19.3%. The ORR was higher for AITL compared to other subtypes (45.5% compared to 23.3% and 15.3% respectively for patients with PTCL-NOS and ALK-negative ALCL). Anemia (10.8%), thrombocytopenia (7%), dyspnea (6.2%), and neutropenia (6.2%) were the most common grade 3 or 4 adverse events. Belinostat was approved by the FDA in July 2014 for the treatment of relapsed or refractory PTCL.

Brentuximab vedotin is an antibody-drug conjugate that targets CD30-expressing malignant cells by binding to CD30 on the cell surface. After internalization, a potent antimicrotubule agent (monomethyl auristatin E) is released within the cell. The safety and efficacy of brentuximab vedotin (IV 1.8 mg/kg every 3 weeks, up to 16 cycles) in patients with relapsed or refractory systemic ALCL was established in a multicenter phase II study (n = 58). Patients had received a median of 2 prior systemic therapies (range, 1–6) and 62% were considered to have primary refractory disease; in addition, 50% of patients were refractory to their most recent prior therapy and 22% had never responded to any therapy. In August 2011, based upon the results from this study, brentuximab vedotin was approved by the FDA for the treatment of patients with systemic ALCL after failure of at least one prior multiagent chemotherapy regimen. Long-term follow-up results confirmed the durability of clinical benefit of brentuximab vedotin in patients with relapsed or refractory systemic ALCL. After a median follow-up of approximately 4 years, the ORR of 83% (62% CR rate) was similar to the previously reported ORR of 86% (59% CR) evaluated by an independent review committee. The estimated 4-year survival rate was 64%. The median duration of objective response for all patients was 13.2 months (the median duration of response for patients with a CR was 26.3 months). The planned subset analysis of phase II multicenter study that evaluated the efficacy and safety of brentuximab vedotin in relapsed/refractory CD30-positive NHL showed that it was also effective in other subtypes of relapsed PTCL particularly AITL. This analysis included 35 patients with PTCL (22 patients with PTCL-NOS and 13 patients with AITL), the ORR, median duration of response and median PFS for all T-cell lymphoma patients were 41%, 7.6 months and 2.6 months respectively. The ORR (54% vs. 33%) and the median PFS (6.7 months vs. 1.6 months) were better for patients with AITL than those with PTCL-NOS.

The combination chemotherapy regimens used for the treatment of relapsed/refractory PTCL (eg. DHAP and ESHAP) are derived from aggressive lymphoma clinical trials that have also included limited number of patients with PTCL and very limited data are available for the specific use of combination chemotherapy regimens in patients with relapsed or refractory PTCL. Aggressive second-line chemotherapy with ICE followed by HDT/ASCR was evaluated in patients with relapsed/refractory PTCL. Among 40 patients treated with ICE, 27 (68%) underwent HDT/ASCR. Based on intent-to-treat analysis, median PFS was 6 months from the time of last ICE therapy; 70% of patients relapsed within 1 year. Patients with relapsed disease had significantly higher 3-year PFS rate compared with those who were primary refractory (20% vs. 6%; \( P = 0.0005 \)). Gemcitabine, dexamethasone and cisplatin (GDP) followed by HDT/ASCR has also been shown to be effective for the treatment of patients with relapsed or refractory PTCL. In a retrospective analysis of 51 patients with relapsed (n = 31) or primary refractory (n = 20) PTCL identified in the BCCA Lymphoid Cancer database, GDP resulted in an ORR of 80% (CR 47%). The 2-
year PFS and OS rates were 25% and 43% respectively, with no differences amongst the histologic subtypes. The median follow-up was 10.4 months. Among patients who were treated subsequently with HDT/ASCR, the 2-year post-transplant OS was 53% with no difference in survival rates between patients with relapsed and refractory disease ($P = .23$). For all non-transplanted patients, the median PFS and OS after treatment with GDP were 4.4 months and 6.8 months, respectively. In another trial that evaluated GDP followed by HDT/ASCR in 25 patients with relapsed/refractory PTCL (14 patients with PTCL-NOS and 4 patients with AITL), the ORR was 72% (48% CR and 24% PR) after a median of 4 cycles of GDP and the median PFS was 9.3 months. The results of a recent retrospective analysis showed that the gemcitabine, vinorelbine and doxorubicin (GND) was effective and well tolerated by patients with refractory or relapsed T-cell lymphomas ($n = 49$; 28 patients with PTCL-NOS), with an ORR of 65.2% and the median OS of 36 months. The 5-year estimated OS rate was 32.4%.  

**NCCN Recommendations**

Participation in a clinical trial is strongly preferred for patients with relapsed/refractory disease. In the absence of a suitable clinical trial, the initial treatment for relapse/refractory disease depends largely on the patient’s eligibility for transplant. Second line systemic therapy followed by consolidation with HDT/ASCR or allogeneic HSCT for those with a CR or PR is recommended for patients who are candidates for transplant. Localized relapse (limited to one or two sites) may be treated with involved-site RT before or after HDT/ASCR. Allogeneic SCT, when feasible, should be considered as a more reliably curative therapy for the majority of patients with relapsed/refractory disease. HDT/ASCR may be an appropriate option for patients, particularly those with ALCL and for selected patients with other subtypes with chemosensitive relapsed disease. Patients who are not candidates for transplant, should be treated with second-line systemic therapy or palliative RT.

Patients who are not candidates for transplant, should be treated with second-line systemic therapy or palliative RT. See “Suggested Treatment Regimens” in the PTCL section of the guidelines for the list recommended treatment options for relapsed/refractory disease.

**Selection of Second-line Systemic Therapy**

Brentuximab vedotin should be the preferred choice for second line therapy for relapsed/refractory ALCL. Belinostat induced responses across all types of PTCL (with the exception of ALK-positive ALCL) and response rates were significantly higher for AITL than other subtypes. Bendamustine also induced higher response rates in patients with AITL compared to those with other subtypes. Pralatrexate has very limited activity in AITL compared to other subtypes. However, the aforementioned studies were not sufficiently powered to evaluate the response rates in specific subtypes. Cyclosporine has been effective in patients with relapsed AITL following treatment with steroid or multiagent chemotherapy or HDT/ASCR.

There is not enough data to support the use a particular regimen for second-line therapy based on the subtype, with the exception of ALCL. The selection of second-line chemotherapy regimen (single agent vs. combination regimen) should be based on the patient’s age, performance status, donor availability, agent’s side effect profile, and goals of therapy. For instance, if the intent is to transplant, ORR or CR rate may be more important than the ability to give a treatment in an ongoing or maintenance fashion without cumulative toxicity. For patients who are intended for transplant soon, combination chemotherapy prior to transplant is often preferred, if HDT/ASCR is being considered. However, for many patients with intention to proceed...
to allogeneic SCT, the use of single agents as a bridge to transplant may be more appropriate because it is necessary to sustain response until a suitable donor is identified and worked up. Combination chemotherapy may be preferred for patients who are ready to proceed to allogeneic SCT when a suitable donor has already been identified. However, if there is no donor available, the use of intensive combination chemotherapy is not recommended due to the inability to maintain a response for longer periods with the continuous treatment. Single agents may also be more appropriate for older patients with a limited performance status or for those patients who are unable to tolerate combination chemotherapy.

Breast Implant-associated ALCL

Lymphomas of the breast are rare, comprising only <0.5% of malignant breast tumors and about 2% of extranodal lymphomas; the majority of cases of NHL of the breast are of B-cell origin.91-93 However, in recent years, numerous cases of primary breast ALCL occurring in association with breast implants have been reported.94-100 In a matched case-control study based on a national pathology registry from the Netherlands, 11 patients with ALCL of the breast were identified over a 17-year time period; pathological and clinical characteristics of these patients were compared with those of control patients (n=30; matched for age and year of diagnosis) with other types of lymphomas in the breast.94 Five of the patients with breast ALCL had received breast implants while one patient in the control group had received an implant prior to lymphoma diagnosis. The odds ratio for ALCL associated with breast implants was 18 (95% CI, 2-157).94 Thus, the probability of developing ALCL was higher among women with breast implants compared with those without implants, although the absolute risk remains very low given the rarity of ALCL of the breast. Based on a literature review of the clinical and histological findings of ALK-negative ALCL associated with breast implants, it has been suggested that breast-implant associated ALCL (BIA-ALCL) may represent a distinct entity from systemic ALCL, but may be more similar to primary cutaneous or indolent ALCL in terms of clinical behavior. Although the majority of reported cases of BIA-ALCL appear to be limited to localized disease, systemic involvement has also been rarely reported.

Given the concern raised by the medical community with regards to breast implants and its putative association with ALK-negative ALCL, the FDA recently conducted a literature-based assessment to better characterize the potential association between implants and ALCL. In the report, the FDA indicated that “women with breast implants may have a very small but increased risk of developing this disease in the scar capsule adjacent to the implant” but that “the totality of evidence continues to support a reasonable assurance that FDA-approved breast implants are safe and effective when used as labeled”.101 At this time, the pathogenesis of ALCL associated with breast implants and the causal effect of such implants remain unknown.

It is becoming recognized that BIA-ALCL is characterized by two distinct clinicopathological presentations associated with different outcomes: in situ BIA-ALCL (anaplastic cell proliferation confined to the fibrous capsule) and infiltrative BIA-ALCL (pleomorphic cells massively infiltrating adjacent tissue).99,102-104 BIA-ALCL presenting in an effusion alone without an associated mass infiltrating through the fibrous capsule (in situ BIA-ALCL) appears to be adequately treated with surgery alone with an excellent long-term survival while BIA-ALCL presenting with a mass have higher rates of relapse.99,102,104 A larger series (87 patients) also confirmed the findings that patients with in-situ BIA-ALCL (the great majority of patients) generally remain free of disease after implant...
removal whereas those with infiltrative BIA-ALCL have higher rates of relapse and may be at higher risk from their disease.\textsuperscript{103} The EFS and OS rates were better for patients with lymphoma confined by the fibrous capsule surrounding the implant compared to patients with lymphoma that had spread beyond the capsule.\textsuperscript{103}

Breast implant-associated ALCL requires individualized care and the aforementioned recommendations for systemic ALCL do not apply to these cases, as the standard of care has not been established. Decisions to remove the unaffected implant or to treat with chemotherapy and/or RT should be made on an individual basis according to the extent of disease involvement. It is generally recommended that upon confirmation of ALCL diagnosis, both the implant and capsule should be removed from the affected breast. In a study of 87 patients with BIA-ALCL, complete surgical excision that consisted of total capsulectomy with breast implant removal was associated with better OS and EFS than partial capsulectomy, systemic chemotherapy, or radiation therapy.\textsuperscript{103} The removal of the implant and the capsule are sufficient for patients with localized disease who present with effusion without a distinct breast mass.\textsuperscript{96-99} In contrast, patients presenting with a mass have higher relapse rates and may require additional therapy. However data to support the benefits of additional therapy and to specify what therapy to add are lacking.\textsuperscript{99,102,105}
References


42. d’Amore F, Relander T, Lauritzen GF, et al. Ten years median follow-up of the NORDIC NLG-T-01 trial on CHOEP and upfront...


55. Horwitz S, Coiffier B, Foss F, et al. Utility of (1)fluorodeoxyglucose positron emission tomography for prognosis and response assessments in a phase 2 study of romidepsin in patients with...


Mycosis Fungoides and Sézary Syndrome

Cutaneous T-cell lymphomas (CTCLs) are a group of NHLs that primarily develop in the skin, and at times progress to involve lymph nodes, blood and visceral organs. In a recent population based study of 3884 cases of cutaneous lymphomas diagnosed during 2001-2005, CTCLs accounted for 71% of cases compared with 29% for cutaneous B-cell lymphomas. Based on data from the SEER program registries for the period 1998 to 2002, the annual incidence rate of CTCL was 9.6 per 1 million persons. Mycosis fungoides (MF) is the most common type of CTCLs. MF accounts for about 50% to 70% of CTCL cases while Sézary syndrome (SS) accounts for only 1% to 3% of cases. MF is an extranodal NHL of mature T-cells with primary cutaneous involvement. SS is an erythrodermic, leukemic variant of CTCL and it is characterized by significant blood involvement and lymphadenopathy. In updated EORTC and WHO classification of CTCL, MF is characterized as an indolent neoplasm.

Large cell transformation (LCT) has been documented in a subgroup of patients with MF and is diagnosed when large cells are present in more than 25% of lymphoid/tumor cell infiltrates in a skin lesion biopsy. Expert hematopathology review is needed to confirm the diagnosis, as LCT may not be easily distinguishable from other lymphoproliferative disorders. The incidence of LCT is strongly dependent on the stage of the disease at diagnosis (1.4% in early-stage disease, compared with 27% for stage IIIB disease and 56%-67% for stage IV disease). In published reports, the median OS from time of diagnosis of LCT ranged between 19 and 36 months. However, in a recent study based on a large cutaneous lymphoma database, the median OS was 8.3 years and the 5-year OS rate was 63% for patients with LCT (n=70). Multivariate analysis from this study showed that LCT was significantly associated with risk of disease progression but not with OS outcomes. LCT is often, but not always, aggressive. CD30 expression of tumor cells is associated with LCT in MF or SS in 30-50% of cases. This finding may have potential implications for CD30-directed therapies.

Prognosis

Published reports have identified the most significant prognostic factors for survival in patients with MF to include age at presentation, extent and type of skin involvement (T classification), overall stage, presence of extracutaneous disease and peripheral blood involvement. Patients diagnosed with limited patch or plaque disease have an excellent prognosis, whereas those with tumor stage disease or erythrodermic skin involvement have a less favorable prognosis; patients with extracutaneous disease have a poor prognosis. Long-term follow-up data from a retrospective cohort study involving 525 patients with MF and SS showed that patient age, T classification, and presence of extracutaneous disease retained independent prognostic value in a multivariate analysis. The risk of disease progression, development of extracutaneous disease or death due to MF was correlated with initial T classification. In a retrospective cohort study of 106 patients with erythrodermic MF and SS, older age, advanced disease and peripheral blood involvement were identified as adverse prognostic factors. Three distinct prognostic groups (favorable, intermediate and unfavorable) were identified according to the number of unfavorable prognostic factors: 65 years or older at presentation, lymph node or visceral (stage IV) disease and peripheral blood involvement were identified as adverse prognostic factors. In a retrospective analysis involving a large number of patients with CTCL (N=1197), the median OS in the group of patients with erythrodermic CTCL (n=124) was 5.1 years (range, 0.4–18.6 years). The extent of blood involvement (as defined by flow cytometric
measurements of Sézary cell counts) was significantly correlated with survival outcomes. In multivariate analysis, advanced age and elevated lactate dehydrogenase (LDH) were the strongest predictors of poor OS.\textsuperscript{13} In a study based on data from patients with MF/SS (N=1502) registered in a large cutaneous lymphoma database, multivariate analysis showed that advanced skin (T) stage, peripheral blood involvement, elevated LDH, and folliculotropic MF were independent factors predictive of increased risk of disease progression and decreased OS.\textsuperscript{8} A recent study reported long-term outcomes in a large cohort of patients with MF/SS (N=1263) from a single center (seen between 1982–2009).\textsuperscript{14} Most patients (71.5\%) presented with early-stage MF (stage IA–IIA) at the time of diagnosis. Median progression-free survival (PFS) and OS was 16 years and 24 years, respectively. Approximately 12\% of patients had disease progression to a higher stage, and 8\% died due to the disease.\textsuperscript{14} Significant independent factors associated with risks for progression or death included age, plaque stage, LDH levels, and tumor area.\textsuperscript{14}

**Diagnosis**

In the algorithms developed by the ISCL, the diagnosis of MF is based on integration of clinical, histopathologic, immunopathologic, and molecular biological characteristics.\textsuperscript{15} According to the revised criteria, significant blood involvement (B2) observed in SS is defined by the presence of T cells with a clonal T-cell receptor (TCR) gene rearrangement in the blood (clonally related to neoplastic T cells in the skin) and either an absolute Sézary cell count of 1000 cells/mcL or more, or increased CD4+ or CD3+ cells with CD4/CD8 ratio of 10 or higher or increased CD4+ cells with an abnormal phenotype (≥ 40\% CD4+/CD7- or ≥ 30\% CD4+/CD26- of total lymphocytes).

Complete skin examination, biopsy of suspicious skin sites and immunohistochemical studies of skin biopsy are essential to confirm the diagnosis. Biopsy of suspicious lymph nodes and assessment of peripheral blood for Sézary cells are recommended in the absence of a definitive skin diagnosis. MF and SS cells are characterized by the following immunophenotype: CD2+, CD3+, CD5+, CD4+, CD8-, CCR4+, CD45RO+ and they lack certain T-cell markers, CD7 and CD26.\textsuperscript{16} There are subtypes of MF that are also CD8+, although rare. If histological evidence of large cell transformation (LCT) is observed, phenotyping with CD30 is recommended. The T-cells also express cutaneous lymphocyte antigen (CLA) and TH2 cytokines. They are also associated with a loss of TH1 and IL-12 cytokines. TCR gene rearrangement should be interpreted with caution since TCR clonal rearrangements can also be seen in non-malignant conditions or may not be demonstrated in all cases of MF/SS. Demonstration of identical clones in skin, blood and/or lymph node may be helpful in selected cases. TCR gene rearrangement analysis by PCR is a useful technique to support the diagnosis of MF/SS and to distinguish MF from inflammatory dermatoses, especially if identical clones are demonstrated in more than one skin sites.\textsuperscript{17} A recent study evaluated the sensitivity and specificity of PCR-based TCRG and TCRB clonality tests in distinguishing MF from inflammatory dermatoses, and reported that the combined use of these tests (in sequence) was more useful than a TCRG test alone; the researchers proposed an algorithm for the sequential use of these tests in patients with intermediate pretest probabilities of having MF.\textsuperscript{18} In at-risk populations, assessment of HTLV-1 status may be useful. HTLV-1 serology can be assessed by ELISA, and if positive, a confirmed by western blot. If the result from western blot is indeterminate, then PCR analysis for HTLV-1 can be performed.
Staging

The TNM staging system developed by the Mycosis Fungoides Cooperative Group (MFCG) had been the standard for staging and classification of patients with MF and SS. Recently, the International Society for Cutaneous Lymphomas (ISCL) and EORTC recommended revisions to the MFCG staging system based on new data that emerged in the area of immunohistochemistry, biology and prognosis of MF and SS following the MFCG publication. In the revised staging system, all staged patients should have a definitive diagnosis of MF and SS. T1 disease is defined as less than 10% of the skin surface involvement with patches or plaques and T4 disease is defined as erythroderma with at least 80% of the skin surface diffusely involved. The extent of skin involvement is based on the percentage of body surface area (BSA) where the patient’s palm (without digits) is equivalent to 0.5% BSA and the palm with all 5 digits is equivalent to 1% BSA. Lymph node biopsy for staging is recommended only for clinically abnormal nodes (>1.5 cm in diameter). However, the designation “Nx” may be used for abnormal lymph nodes without histologic confirmation. Visceral disease with the involvement of an organ (e.g., spleen, liver) other than the skin, nodes or blood should be documented using imaging studies. The designation “Mx” can be used for presence of abnormal visceral sites without histologic confirmation.

Blood involvement is classified into three groups: B0 is associated with the absence of significant blood involvement (5% or less of Sézary cells); B1 is defined as having a low tumor burden (more than 5% of Sézary cells but does not meet the criteria for B2); B2 is associated with high tumor burden with more than 1000 Sézary cells/mcL or increase in CD4+ cells with an abnormal phenotype (≥40% CD4+/CD7- or ≥30% CD4+/CD26- of total lymphocytes). According to the updated staging system, patients with stage III are further divided into two subgroups, stages IIIA and IIIB, to differentiate based on the extent of blood involvement (B0 and B1, respectively).

Workup

The initial workup of patients diagnosed with MF or SS involves a complete skin examination to assess the extent of the disease (i.e., percent of BSA), type of skin lesion (e.g., patch/plaque, tumor, erythroderma), and examination of lymph nodes or other masses for the evaluation of lymphadenopathy or organomegaly. Laboratory studies should include CBC with Sézary screen (manual slide review to identify Sézary cells) and flow cytometry to assess for expanded CD4+ cells with increased CD4/CD8 ratio or with abnormal immunophenotype. A comprehensive metabolic panel and assessment of LDH levels should also be part of the initial laboratory studies. Analysis of TCR gene arrangement of peripheral blood lymphocytes is recommended if blood involvement is suspected. Patients with unfavorable features (T2 or higher, folliculotropic MF or large cell transformation, palpable adenopathy or abnormal laboratory studies) should undergo either CT or PET-CT scan of the chest, abdomen and pelvis. A CT scan of the neck may be useful in some circumstances. Integrated PET-CT was found to be more sensitive for the detection of lymph node involvement than CT alone and can help direct biopsies. Bone marrow biopsy is not required for disease staging, but may be helpful in those with suspected marrow involvement (include B2 blood involvement) or in those with an unexplained hematologic abnormality. Biopsy of suspicious lymph nodes (i.e., palpable nodes >1.5 cm in diameter and/or firm, irregular, clustered or fixed nodes) is recommended with evaluation for TCR gene rearrangements, especially due to the worse prognosis of patients with clonal rearrangement in lymph nodes.
T-cell Lymphomas

Initial treatment in patients with patch/plaque disease consists of skin-directed therapies (localized or generalized), with the addition of milder systemic therapy ("SYST-CAT A"; see Guidelines page MFSS-A) for refractory, persistent, or progressive disease with skin-directed therapies. Those patients who have unfavorable prognostic features (e.g., folliculotropic or large-cell transformed MF, or B1 involvement) may have systemic therapies introduced earlier in the treatment algorithm. Patients who do not respond to biologic therapy or those with very aggressive or extracutaneous disease may be treated with chemotherapy. Due to the rarity of the condition and the need for an individualized approach, referral to a multidisciplinary academic specialty center is preferred.

Skin-directed therapies

Localized skin-directed treatments include topical therapy with corticosteroids, mechlorethamine hydrochloride, carmustine, topical retinoids (e.g., bexarotene) or topical imiquimod, or local radiation therapy (RT). Generalized skin-directed therapies such as phototherapy [UVB or PUVA (psoralen and UVA)] and total skin electronic beam therapy (TSEBT) are indicated in patients with widespread skin involvement (see Guidelines page MFSS-A under “Skin-directed therapies”).

Topical corticosteroids are effective, especially for the treatment of patch-stage MF, producing response rates of over 90%. However, long-term use of topical steroid may lead to skin atrophy or striae formation and the risk becomes greater with increased potency of the steroid. Moreover, high-potency steroid used on large skin surfaces may lead to systemic absorption. Topical chemotherapy with nitrogen mustard or carmustine has been used for the management of MF for many decades. Long-term follow-up results from a retrospective cohort study in 203 patients with stage I-III MF have confirmed the activity and safety of topical therapy with this approach. The overall response rate (ORR) was 83% (complete response [CR] in 50%). The 5-year relapse-free survival rate for patients with a CR was 42%. The median overall survival (OS) for the entire cohort was 16 years and the actuarial 10-year OS rate was 71%. The efficacy with topical nitrogen mustard was similar for aqueous and ointment preparations, although the ointment was associated with reduced hypersensitivity reactions. Patients with T1 disease had higher ORR (93% vs. 72%) and CR rate (65% vs. 34%) than those with T2 disease. Moreover, patients with T1 disease had longer median OS (21 months vs. 15 months) and 5-year OS rate (97% vs. 72%) compared with patients with T2 disease. A multicenter randomized phase II trial evaluated the efficacy of a topical gel formulation of the nitrogen mustard mechlorethamine compared with the compounded ointment formulation in patients with stage IA or IIA MF (N=260). Eligible patients had not been treated with topical mechlorethamine within 2 years of study enrollment and had not received prior therapy with topical carmustine. Response rate based on Composite Assessment of Index Lesion Severity was 58.5% with the gel formulation compared with 48% for the ointment; these outcomes met non-inferiority criteria for the gel formulation arm. No study treatment-related serious adverse events were reported, and no systemic absorption was detected.

Synthetic retinoids (bexarotene and tazarotene) and imiquimod have been used as topical therapy for the treatment of patients with MF and SS. FDA-approved bexarotene gel was evaluated in two open-label, historically-controlled clinical studies involving 117 patients with CTCL. In the phase I-II trial involving 67 patients with early stage MF, the ORR was 63% (CR in 21%); the estimated median response
duration was 99 weeks.\textsuperscript{33} Response rates were higher among the patients who had no prior therapy compared with those who had received prior topical therapies (75\% vs. 67\%). In the phase III multicenter study of 50 patients with early stage refractory MF, the ORR was 44\% (CR in 8\%).\textsuperscript{34} In a small open-label pilot study in patients (N=20) with early patch or plaque MF lesions (stable or refractory to therapy), tazarotene 0.1\% topical gel was reported to be a well-tolerated and active adjuvant therapy by clinical and histologic assessments.\textsuperscript{35} In a small number of case studies, imiquimod was active in patients with early stage MF refractory to other therapies.\textsuperscript{36-38} Bexarotene gel is the only FDA approved synthetic retinoid for topical therapy in patients with MF and SS. Given the common skin irritation toxicity observed with topical retinoids and imiquimod, these agents are best for treatment of localized, limited areas.

MF is extremely radiosensitive and patients with minimal stage IA MF may be managed effectively with local superficial RT without adjuvant therapy.\textsuperscript{39} High disease-free survival (DFS) rates (75\% at 5 years; 64\% at 10 years) have been reported for patients with early stage disease treated with RT alone (N=21).\textsuperscript{40} The 10-year DFS rate was 85\% for patients with unilesional disease. The optimal RT dose was at least 20 Gy, which resulted in a DFS rate of 91\% with no distant failures. In another report in patients with unilesional MF (n=18), treatment with local RT (most patients received RT dose of 30.6 Gy) resulted in an ORR of 100\%, with a 10-year relapse-free survival (RFS) and OS rates of 86\% and 100\%, respectively.\textsuperscript{41} TSEBT has been shown to be effective in patients with early stage MF, without the need for adjuvant therapy.\textsuperscript{42} In patients with T1 or T2 disease (N=57) treated with TSEBT (mean total RT dose of 30 Gy), the ORR was 95\%; CR was observed in 87.5\% and 85\% of patients with T1 and T2 disease, respectively.\textsuperscript{42} After a median follow up of 114 months, the 5-year DFS and OS rates were 50\% and 90\%, respectively. The 10-year OS rate was 65\%.\textsuperscript{42} TSEBT has also been shown to be active in patients with thick generalized plaque (T2) or tumorous disease (T3). In a retrospective analysis involving 148 patients with T2 and T3 disease, TSEBT alone or in combination with adjuvant topical mechlorethamine hydrochloride yielded significantly higher CR rates compared with mechlorethamine hydrochloride alone (76\% vs. 39\% for T2; 44\% vs. 8\% for T3).\textsuperscript{43} The standard dose of TSEBT is 30-36 Gy (given in fractions over 8 to 10 weeks), but recent studies suggest that lower radiation doses may be sufficiently active. A recent retrospective study in patients with T2 to T4 disease (N=102; excluded patients with extracutaneous disease) treated with TSEBT doses of 5 to <30 Gy showed ORR (>50\% improvement) of 96\% and CR rate of 31\%.\textsuperscript{44} The ORR among the subgroup that received 5 to <10 Gy (n=19), 10 to <20 Gy (n=52), and 20 to <30 Gy (n=32), were 90\%, 98\% and 97\%, respectively. The CR rate with TSEBT 5 to <30 Gy was higher among patients with T2 compared with T3 disease (41\% vs. 17\%).\textsuperscript{44} In patients with T2 or T3 disease, OS and PFS outcomes were not significantly different by dose groups and were comparable to that of standard dose TSEBT (i.e., ≥30 Gy).\textsuperscript{44} The lower dose ranges with TSEBT 10 to <20 Gy warrants further evaluation, especially in combination regimens. In a recent prospective study, patients with stage IB-IV MF (N=10) were treated with TSEBT 1 Gy weekly (for a total dose of 10 Gy).\textsuperscript{45} The ORR was 90\% and 70\% achieved a CR or very good partial remission (PR)<1\% skin affected by patches/plaques). The median duration of response was 5 months. Low dose of TSEBT was well tolerated in this patient population; further studies of its use in combined modality regimens are warranted.

Phototherapy with UVB (including narrowband) and photochemotherapy with psoralen and UVA (PUVA) are effective alternative treatment
options for patients with early stage MF. In a retrospective analysis of patients with stage IA or IB (N=56), phototherapy with narrowband UVB (n=21) and PUVA (n=35) produced similar CR rates (81% vs. 71%) and mean relapse-free interval (24.5 months vs. 23 months). In another retrospective study in a larger group of patients with early-stage MF (stages IA–IIA; N=114), treatment with narrowband UVB (n=19) and PUVA (n=95) also resulted in similar CR rates (68% vs. 62%) and median time to relapse (11.5 months vs. 14 months). In a retrospective analysis of long-term follow-up data from patients with early-stage MF (stages IA–IIA) who achieved a CR with PUVA (N=66), 10-year DFS rates were 30% for patients with stage IA disease and 50% for those with stage IB/IIA disease. The median follow-up time was 94 months. The 10-year OS rates were 82% and 69%, respectively; interestingly, OS outcomes were not different by relapse status. A third of patients developed signs of chronic photodamage and secondary cutaneous malignancies. It should be noted that cumulative doses of UV are associated with increased risk of UV-associated skin malignancies. Thus, phototherapy may not be appropriate for patients with a history of squamous or basal cell carcinoma or melanoma. Since narrowband UVB has less skin toxicity than broadband and PUVA, it is preferred to start with narrowband UVB than PUVA in early-stage patients with patch or thin plaque disease.

**Systemic therapies**

There are extensive data—although primarily from small clinical studies—on many systemic therapeutic options for CTCL. Historically, the response criteria for CTCL were poorly defined and validated response assessments were lacking. More recent studies have incorporated consensus response assessments and newer FDA-approved agents have undergone central review for efficacy outcomes. Systemic therapies with extracorporeal photopheresis (ECP), interferons, systemic retinoids, or histone deacetylase (HDAC) inhibitors are preferred over traditional chemotherapy for patients who do not respond to initial skin-directed chemotherapy (see Guidelines page MFSS-A under “SYST-CAT A”). Multiagent chemotherapy is generally reserved only for patients who do not respond to multiple prior therapies (including single-agent chemotherapy and combination regimens) or those with bulky lymph node or solid organ disease. In the absence of other unfavorable prognostic features, it is recommended that systemic therapy be deferred until the patient has failed multiple treatments with local and skin-directed therapy.

ECP is an immunomodulatory therapy using psoralen and UVA extracorporeally. This approach involves the removal of leukocytes by leukapheresis, which are then treated with 8-methoxypsoralen, exposed to UVA and returned to the patient. ECP is a long standing treatment for MF, and is particularly indicated in patients with or at risk of blood involvement (erythrodermic stage III disease or IVA with SS). In small retrospective studies with ECP (generally given for at least 6 months) in patients with CTCL, ORR ranged from about 50-70% with a CR in 15-25%; median OS was 6-8 years, and 5-year OS rate was reported to be 80% in one study. In a meta-analysis of 19 studies (5 studies using ECP as monotherapy and 14 studies as combination therapy) involving more than 400 patients with CTCL, the combined ORR for all stages of CTCL was 56% with 18% achieving a CR. ECP as monotherapy resulted in 55.5% ORR with 15% CR. The corresponding response rates were 58% (15% CR) for erythrodermic disease (T4) and 43% (9.5% CR) for SS. Studies evaluating combination regimens with ECP are discussed below, in the section “Combination Therapies”.
Retinoids [all-trans retinoic acid (ATRA), 13-cis retinoic acid and their synthetic analogs acitretin and isotretinoin] and interferons have been used for many years for the treatment of CTCL.\textsuperscript{55,56} Interferon (IFN) alpha as a single agent has produced ORR greater than 70% with CR rates greater than 20%.\textsuperscript{55} IFN gamma has been shown to be effective in the treatment of patients with various stages of CTCL that is refractory to IFN alpha and other topical or systemic therapies.\textsuperscript{57}

Oral bexarotene has been evaluated for the treatment of refractory or persistent early- and advanced-stage CTCL in two multicenter clinical trials.\textsuperscript{58,59} In patients with early-stage CTCL (stages IA-IIA) refractory to prior treatment, bexarotene was well tolerated and induced an ORR of 54% among patients treated at doses of 300 mg/m\textsuperscript{2}/day (n=28).\textsuperscript{59} The rate of disease progression at this dose was 21%, and the median duration of response had not been reached at the time of the report. In patients with advanced CTCL (stages IIB–IVB) refractory to prior treatments, clinical CR and PR were observed in 45% of patients receiving 300 mg/m\textsuperscript{2}/day (n=56). At doses greater than 300 mg/m\textsuperscript{2}/day (n=38), the ORR was 55%, including 13% clinical CR.\textsuperscript{58} Side effects were reversible and manageable with appropriate medications prior to initiation of treatment. In a retrospective comparison study, ATRA and bexarotene were reported to induce similar outcomes with modest single-agent activity in the treatment of patients with relapsed MF and SS.\textsuperscript{60} Bexarotene (oral capsules) is approved by the FDA for the treatment of refractory CTCL.

HDAC inhibitors are a new class of drugs that are potent inducers of histone acetylation, cell cycle arrest and apoptosis. The activity and safety of the HDAC inhibitors vorinostat and romidepsin were evaluated in patients with refractory CTCL in phase II trials.\textsuperscript{61-64} In a phase IIb study involving 74 patients (median 3 prior therapies) with persistent, progressive or refractory stage IB to IVA MF/SS, vorinostat resulted in an ORR of 30% and median time to progression of 5 months.\textsuperscript{62} Median time to progression was greater than 9.8 months in responders with advanced disease (stage IIB or higher).\textsuperscript{62} The response rates and median response durations appeared to be comparable to those obtained with bexarotene capsules and denileukin diftitox. Vorinostat was the first HDAC inhibitor to receive FDA approval for the treatment of patients with progressive, persistent, or recurrent CTCL, on or following two systemic therapies. A post-hoc subset analysis of patients who experienced clinical benefit with vorinostat in the previous phase IIb study and received 2 or more years of vorinostat therapy (n=6) provided some evidence for the long-term safety and clinical benefit of vorinostat in heavily pretreated patients, regardless of previous treatment failures.\textsuperscript{65}

Romidepsin demonstrated single-agent activity in 2 open-label clinical studies [pivotal phase 2B study (GPI-04–0001) and NCI 1312 (supportive study)] of 167 patients with CTCL refractory to prior therapies.\textsuperscript{64,66} The pivotal phase IIb study (GPI-04-0001) enrolled 96 patients with stage IB to IVA CTCL (71% had advanced stage disease ≥ stage IIB; median 2 prior systemic therapies).\textsuperscript{64} The ORR was 34% (CR in 6%). Among patients with advanced stages of disease, 38% achieved an objective response (CR in 7%).\textsuperscript{64,67} The median time to response was 2 months and the median duration of response was 15 months. Improvement in pruritus was observed in 28 of 65 patients (43%) with moderate to severe symptoms at baseline, including in 11 patients who did not achieve an objective response.\textsuperscript{67} These results are consistent with the findings of the phase NCI 1312 (supportive study) in a similar population (N=71) using the same dose and schedule of romidepsin, where the ORR was 34% (CR in 7%) and the median duration of response was 14 months.\textsuperscript{68} In the pivotal study, romidepsin also induced clinically significant responses in patients with blood
involvement. Among evaluable patients (n=27), the ORR was 32% by composite assessment, including 2 clinical CRs. In a pooled analyses of these two international multicenter clinical studies, objective response was seen 41% of patients (CR in 7%) in the evaluable population (patients who had at least 2 cycles of romidepsin; n=135). Responses were noted in 42% of patients with stage IIB or greater MF and 58% of patients with SS. Median duration of response and median time to disease progression were 15 months and 8 months, respectively. Romidepsin is approved by the FDA for the treatment of CTCL in patients who have received at least one prior systemic therapy.

Denileukin diftitox is a recombinant fusion protein with interleukin-2 (IL-2) and diphtheria toxin, and targets the high-affinity IL-2 receptor (CD25) expressed on malignant T-cells and B-cells. Although denileukin diftitox was FDA approved for the treatment of patients with persistent or recurrent CTCL based on phase III studies, the agent is currently not available (as of June 2012); the manufacturer recently terminated a phase III study in PTCL to prioritize the development of a new improved formulation of the drug.

Conventional cytotoxic systemic chemotherapy is used as a primary treatment only for patients with advanced disease, i.e., stages IIB-IV (see Guidelines page MFSS-A for treatments under “SYST-CAT-B” and “SYST-CAT-C”) or large cell transformation (see pages MFSS-6 and MFSS-A for treatments under “SYST-CAT-C”) and for second-line therapy for early-stage disease refractory to skin-directed therapies and systemic biologic therapies (see page MFSS-5 for refractory disease). Low-dose methotrexate has been used to treat early-stage MF and SS for many years, although only limited data are available.

Gemcitabine as a single agent has been evaluated in patients with advanced, heavily pretreated CTCL and as front-line therapy in untreated patients. Another nucleoside analog pentostatin has shown activity either as a single agent or in combination with IFN alpha in patients with advanced MF or SS. Limited data also suggest some activity for the oral alkylating agent temozolomide and the proteasome inhibitor bortezomib in patients with previously treated MF.

Pegylated liposomal doxorubicin has shown substantial single-agent activity in patients with pretreated, advanced or refractory CTCL. In a small prospective phase II trial in patients with previously treated CTCL (N=19; MF, n=13 [including transformed MF in n=3]; SS, n=3), pegylated liposomal doxorubicin induced an ORR of 84% (CR in 42%) with no significant differences between patients with stage I-IIA and IIB-IV disease. After a median follow up of 23 months, the median event-free survival and OS was 18 months and 34 months, respectively. In another prospective study in patients with advanced or refractory MF/SS (N=25), the ORR was 56% (CR in 20%) with pegylated liposomal doxorubicin. The median OS was 44 months. A phase II multicenter trial from the EORTC evaluated pegylated liposomal doxorubicin in patients with advanced MF (stage IIB, IVA, IVB) refractory or relapsed after at least 2 prior systemic therapies (N=49). The ORR was 41% (CR in 6%). The median time to progression was 7 months and the median duration of response was 6 months. Single-agent therapy with pegylated liposomal doxorubicin was well tolerated with no grade 3 or 4 hematologic toxicities; the most common grade 3 or 4 toxicities included dermatologic toxicity other than hand and foot reaction (6%), constitutional symptoms (4%), gastrointestinal toxicities (4%) and infection (4%). A recent phase II study evaluated pegylated liposomal doxorubicin followed sequentially by oral bexarotene in patients with advanced-stage or refractory CTCL (N=37; stage IV, n=21 [including SS, n=7]; stage IIB, n=10; refractory, n=6). Treatment with 8 doses (16 weeks) of liposomal doxorubicin resulted in an ORR of 41%
including clinical CR in 2 patients (n=34 evaluable). The maximum response was observed after 16 weeks of treatment with liposomal doxorubicin; sequential bexarotene did not improve the response rate or duration. At the time of follow up (median 7.5 months for surviving patients), the median PFS was about 5 months.87

Pralatrexate is a folate analog indicated for patients with relapsed/refractory peripheral T-cell lymphoma (PTCL), and has also demonstrated activity in patients with CTCL. In a multicenter dose-finding study, pralatrexate 10 mg/m² to 30 mg/m² (given weekly for 2 of 3 weeks or 3 of 4 weeks) was evaluated in patients with relapsed or refractory CTCL (N=54; MF, n=38 [70%]; SS, n=15 [28%]).88 Patients had received a median of 4 prior systemic therapies (range, 1–11). The recommended dose was identified as 15 mg/m² weekly for 3 weeks of a 4-week cycle. The ORR for all evaluable patients on this study was 41% (CR in 5.5%). Among the patients (in the dose-finding cohort and expansion cohort) who received the recommended dose (as above; n=29), the ORR was 45% (CR in 3%).88 Thus, low-dose pralatrexate was shown to have high activity in patients with heavily pretreated CTCL.

Based on limited data from clinical studies and case report, liposomal doxorubicin, denileukin diftitox and gemcitabine have shown some activity in patients with transformed MF.85,89,90 In the subgroup of patients with relapsed/refractory transformed MF (n=12) treated on the PROPEL trial that evaluated pralatrexate (30 mg/m² weekly for 6 weeks of a 7-week cycle) in patients with PTCL, the ORR based on investigator assessment and by independent review was 58% and 25%, respectively.91,92 Based on investigator assessment, the median duration of response was 4 months and median PFS was 5 months. The median OS was 13 months.91

Combination therapies
Combinations of biologic or non-cytotoxic therapies as distinct from combination chemotherapies are used when single-agent therapies fail or in cases of advanced, progressive, or refractory disease (see Guidelines page MFSS-A for regimens under “Combination Therapies”). The rationale for such systemic combination strategies in CTCL is to provide synergistic efficacy without additive toxicities. Combinations of systemic agents with skin-directed therapies are often used to maximize clinical responses in the skin compartment. Several combination therapies have been studied in clinical trials for CTCL. Most commonly used combination regimens include phototherapy plus either IFN or systemic retinoid, and ECP plus either IFN or systemic retinoid or both.93-99 PUVA when used in combination with IFN alfa produced an ORR of 93% (CR in 80%) in patients with stage IB to stage IVB disease evaluated in a phase I trial (N=15); the median duration of response exceeded 23 months.93 In a prospective randomized study evaluated IFN combined with PUVA versus IFN combined with retinoids in patients with stage I or II CTCL (N=82 evaluable), the combination of IFN with PUVA resulted in significantly higher CR rates in this patient population (70% vs. 38%).97 In a phase II trial in patients with symptomatic MF/SS (N=63; stages IA-IIB, n=43; stages IIA-IIB, n=6; and stages III-IVA, n=14). IFN combined with PUVA (followed by PUVA maintenance in patients with a CR) resulted in a CR in 75% of patients, with a median duration of response of 32 months.99 The 5-year DFS and OS rates were 75% and 91%, respectively. In another prospective phase II trial in patients with early-stage MF (stages IA-IIB; N=89), the combination of low-dose IFN alfa with PUVA resulted in an ORR of 98% (CR in 84%).94 Low-dose bexarotene in combination with PUVA also resulted in high response rates with an ORR of 93% (CR in 47%) in a small group of patients with MF/SS (all stages) resistant or intolerant to previous therapies (N=15).100 However, a phase III randomized study
from the EORTC recently reported no significant differences in outcomes using the combination of bexarotene with PUVA compared with PUVA alone in patients with early stage MF (stage IB and IIA; N=93).\textsuperscript{101} The ORR with the combination was 77% (CR in 31%) compared with 71% (CR in 22%) with PUVA alone; the median duration of response was 5.8 months and 9.7 months, respectively. A trend towards fewer PUVA sessions and lower UVA doses to achieve CR was observed with the combination arm, although the differences were not significant.\textsuperscript{101} This trial was closed prematurely due to low patient accrual.

The combination of biologic agents with ECP has been shown to improve response rates in patients with advanced stage CTCL.\textsuperscript{53,98,102} In a retrospective study involving patients with advanced CTCL (N=47), ECP with or without biologic agents (i.e., IFN, systemic retinoids, sargramostim) resulted in an ORR of 79% (CR in 26%) with a median OS of 74 months.\textsuperscript{98} The median OS in the subgroup of patients with stage III or IV disease with blood involvement was 55 months. The combined modality therapy (ECP with IFN and/or systemic retinoids) resulted in improved response rates (84% vs. 75%) and median OS (74 months vs. 66 months) compared with ECP alone despite poor prognostic features among patients treated with combined modality therapy; these differences in outcomes were not statistically significant, however.\textsuperscript{98} In a recent retrospective cohort study of patients with SS (N=98) who received at least 3 months of ECP combined with 1 or more biologic agents (i.e., IFN alfa, systemic retinoid, IFN gamma, and/or GM-CSF), the ORR was 75% with CR in 30% of patients.\textsuperscript{102} Most patients on this study received ECP in combination with IFN alfa (89%) and/or systemic retinoids (86%); 30% of the patients were treated with ECP combined with both IFN alfa and systemic retinoids. The 5-year OS rate from time of diagnosis was 55% and the median OS was 65%.\textsuperscript{102} The 5-year OS rates for the subgroups of patients with stage IIIB, IVA1, IVA2, and IVB were 80%, 80%, 76%, and 0%, respectively. A higher monocyte percentage at baseline was significantly associated with CR rates.\textsuperscript{102}

Systemic retinoids have been studied in combination with other biological response modifiers in patients with advanced disease. The combination of low-dose bexarotene and low-dose IFN alfa was reported to have synergistic activity in a small case series of patients with CTCL (erythrodermic CTCL and follicular MF).\textsuperscript{103} In a phase II study in patients with CTCL (N=22; all stages) oral bexarotene (at standard doses; 300 mg/m\textsuperscript{2}/day for at least 8 weeks) was evaluated in combination with IFN alfa (added in cases of <CR after 8 weeks of bexarotene alone).\textsuperscript{104} Among evaluable patients (n=18), the ORR for the combined regimen was 39% (CR in 6%). Although the regimen was well tolerated, response rates were not improved relative to the ORR expected with bexarotene alone.\textsuperscript{58,59} The combination of bexarotene and denileukin diftitox is particularly interesting given that bexarotene has been shown to increase CD25 expression in CTCL cells, thereby potentially increasing the susceptibility of T-cells to denileukin diftitox. In a phase I study in patients with relapsed/refractory CTCL (N=14), denileukin diftitox combined with bexarotene resulted in an ORR of 67% (CR in 28.5%).\textsuperscript{105} Lastly, combined modality therapy with oral isotretinoin and IFN alfa (followed by TSEBT and maintenance therapy with topical nitrogen mustard and IFN alfa) was evaluated in patients with MF (N=95; stages IA-IIA, n=50; stages IIB-IVB, n=45) in a long-term follow-up study.\textsuperscript{106} The ORR was 85% with CR in 60% of patients; the CR rate was 76% among patients with early-stage MF (remission >5 years in 24% of responders) and 40% among those with advanced stage disease (remission >5 years in 17%). The median DFS and OS rate for patients with early-stage disease was 62 months and
145 months, respectively. The corresponding endpoints for patients with advanced stage disease were 7 months and 36 months, respectively. The 5-year estimated OS rate was 94% for patients with early-stage and 35% for advanced-stage MF. Disease stage was the only independent prognostic factor for survival based on multivariate analysis.106

NCCN Recommendations Based on Clinical Stage

Primary Treatment

The NCCN Guidelines panel recommends that patients diagnosed with MF/SS be treated at specialized centers with expertise in the management of this disease. It should be noted that unlike other NHL subtypes, response criteria for MF/SS has not been shown to correlate with prognosis. The decisions to continue with or switch treatment regimens are often made based on clinical parameters. A proposal for detailed response criteria for MF/SS, according to consensus from an international group of experts, was recently published.21

Patients with stage IA disease have an excellent prognosis using skin-directed therapies alone, where their life expectancy is not altered compared with matched control populations.8,12 Stage IA is managed primarily with skin-directed therapies, alone or in combination with other skin-directed therapies including local RT (see page MFSS-4). Local RT (12–36 Gy) is recommended particularly for unilesional presentation. Treatment options include topical corticosteroids, topical chemotherapy (i.e., nitrogen mustard or carmustine), topical retinoids (i.e., bexarotene or tazarotene), topical imiquimod, and/or phototherapy (UVB for patch or thin plaques; PUVA for thicker plaques) (see page MFSS-A). Patients with a PR to initial therapies (i.e., having persistent T1 skin disease) should be treated with other options from the list of recommendations therapies mentioned above.

Patients with stage IB-IIA disease require generalized skin treatment (see page MFSS-5). Topical retinoids are not recommended for generalized skin involvement because these treatments can cause substantial irritation. In addition to the other skin-directed therapies used for stage IA disease (as mentioned above), TSEBT (12–36 Gy) is another treatment option for those with severe skin symptoms or generalized thick plaque or tumor disease (see page MFSS-A. Although TSEBT is highly effective in T1 disease (stage IA), it is reserved for generalized or recalcitrant skin disease due to its toxicities and lack of superior long-term outcome. It is common practice to follow TSEBT with systemic therapies such as interferon or bexarotene to maintain response. For patients with sites that are not responsive to generalized treatment, additional treatment may be needed. Patients with persistent T1 skin disease should be treated with skin-directed therapies as mentioned for patients with stage 1A disease; patients with persistent T2 disease should be treated with other options from the list of treatments for generalized skin involvement, as mentioned above.

Patients with stage IB-IIA disease with B1 blood involvement are often best managed with more intensive treatments as described for stage III with B1 blood involvement (see Discussion below). Patients with histological evidence of folliculotropic or large cell transformation (LCT) are usually managed as described for treatment of stage IIB disease (see Discussion below).

Patients with stage IIB disease and/or histological evidence of folliculotropic or LCT can be separated into two categories: 1) limited extent tumor disease with or without patch/plaque disease; or 2) generalized tumor disease, transformed and/or folliculotropic disease (see page MFSS-6). In patients with tumor disease, rebiopsy is necessary if LCT is suspected. Patients with limited extent tumor disease can be managed with local RT for tumor lesions. Combination
or adjuvant systemic therapy (SYST-CAT A: retinoids, IFNs, HDAC inhibitors, ECP, methotrexate [≤100 mg per week]) may be considered to improve overall response and duration of response. Skin-directed therapies, as described above for stage I-IIA disease, can be used for residual patch or plaque lesions.

Patients with generalized tumor disease are treated with TSEBT or systemic therapy, with or without skin-directed therapy. For patients treated with TSEBT, adjuvant therapy with systemic therapies (SYST-CAT A) can be considered to improve response duration. For systemic therapy, recommended options include treatments listed under SYST-CAT A (as listed above), SYST-CAT B (first-line: liposomal doxorubicin, gemcitabine; second-line: chlorambucil, pentostatin, etoposide, cyclophosphamide, temozolomide, methotrexate [≥100 mg per week], bortezomib, low-dose pralatrexate), or SYST-CAT C (liposomal doxorubicin, gemcitabine, romidepsin, low-dose or standard-dose pralatrexate, regimens recommended for PTCL in the NHL Guidelines), or combination therapies.

Systemic therapy is the initial treatment for patients with LCT (see pages MFSS-6 and MFSS-A). If there is no evidence of aggressive growth, systemic therapies from SYST-CAT A or SYST-CAT B are appropriate. Patients with indolent/plaque folliculotropic MF (without evidence of LCT) should initially be considered for options under SYST-CAT A before resorting to treatment options listed under SYST-CAT B or SYST-CAT C. For LCT with aggressive growth, the NHL Guidelines panel recommends systemic therapy with options listed under SYST-CAT C). Combination regimens are generally reserved for patients with relapsed or refractory or extracutaneous disease. Following completion of primary therapy, patients with persistent T1 or T2 disease should be treated with skin-directed therapies for limited (T1) or generalized (T2) skin involvement. Patients with persistent T3 limited extent disease should continue to receive local RT with adjuvant systemic therapy (SYST-CAT A), or systemic therapy (with or without skin-directed therapies and with or without RT). Patients with persistent T3 disease should continue to receive TSEBT, systemic therapies, or combination therapies, with or without skin-directed therapies.

Management of patients with stage III disease depends on the extent of blood involvement (see page MFSS-7): no significant blood involvement (B0) or some blood involvement (B1), which is less than that observed for SS (B2). Patients with no significant blood involvement are treated with generalized skin-directed therapies similar to those recommended for stage IB -IIA (see page MFSS-A). Generalized skin-directed therapies should be used with caution in patients with stage III disease, as treatments other than topical steroids may not be well tolerated. Phototherapy (PUVA or UVB) or TSEBT may be used successfully in these patients. ECP may be a more appropriate systemic therapy for patients with stage III disease with blood involvement. Alternative options include other treatment options listed under SYST-CAT A, with or without skin-directed therapy. Mid-potency steroids should be used in combination with systemic therapy to reduce skin symptoms. Antibiotic therapy should be considered for this group of patients since they are at increased risk of developing secondary infections. Patients with inadequate response or persistent disease should be treated with other options within the list of primary treatments (generalized skin-directed treatments or for blood involvement, SYST-CAT A with or without skin-directed therapy).

Stage IV disease includes SS and non-Sézary or visceral (solid organ) disease. SS patients are treated with single agent systemic therapy (agents listed in SYST-CAT A) or combination therapies (see pages MFSS-8 and MFSS-A). Safety data on the use of systemic retinoids in combination with TSEBT and vorinostat in combination with
phototherapy or TSEBT is currently lacking. Non-Sézary or solid organ disease is frequently managed with systemic therapy (SYST-CAT B or SYST-CAT C) with or without RT for local control. These patients may present with more aggressive growth characteristics. If there is no evidence of aggressive growth, systemic therapies from SYST-CAT B would be more appropriate. In cases where aggressive growth is observed, the regimens listed under SYST-CAT C would be preferred. Adjuvant biologic therapy may be considered following chemotherapy to improve response duration.

All patients (stage IA through stage IV) showing response (and/or clinical benefit) should be considered for maintenance or tapering therapy to optimize response duration. Patients with a PR or disease relapse following primary treatment should be treated with the other options included in the primary treatment to improve response before starting treatment for refractory disease. In addition, patients with disease relapse or persistent disease may be considered for clinical trials. Patients with stage IV disease should be considered for clinical trials.

Refractory, Progressive, or High-Risk/Advanced Disease

Role of Allogeneic Stem Cell Transplantation

Autologous stem cell transplantation (SCT) has been used infrequently for patients with CTCL. In general, the duration of response have been short, thus limiting its utility and uptake. Allogeneic SCT has been reported only in case reports or small series in patients with advanced MF and SS, or in retrospective studies. Several of these published cases reported on the association between graft-versus-host disease and tumor response, or the reinduction of remission following withdrawal (or reduction) of immunosuppression, suggesting that graft-versus-tumor effect may play an important role in the extent of disease control achieved with allogeneic SCT. A meta-analysis compared the outcome of allogeneic versus autologous SCT in patients with MF and SS based on patient cases derived from the literature. The analysis suggested that OS outcomes and response durations were more favorable among the patients who received allogeneic SCT. In the allogeneic SCT group, the majority (70%) of patients experienced persistent graft-versus-host disease (GVHD), which was primarily mild to moderate in severity. Whereas the majority of the deaths among patients undergoing autologous SCT may be attributable to progressive disease, deaths associated with allogeneic SCT may be more due to non-relapse mortality (NRM). The incidence of NRM in published reports with allogeneic SCT is about 21% to 25%. In a study that evaluated TSEBT with allogeneic HSCT in patients with advanced CTCL (N=19), the ORR was 68% (CR in 58%) with median OS not reached at the time of the report; the TRM rate was 21%. In a retrospective analysis of patients with MF/SS registered in the EBMT database (N=60), the 3-year PFS and OS rate with allogeneic SCT was 34% and 54%, respectively. The NRM rate at 2 years was 22%. Outcomes were not significantly different between histology types. However, patients with advanced-stage disease had a higher 3-year relapse rate compared with those with earlier stage disease (53% vs. 25%; P=0.02). The use of reduced-intensity conditioning was associated with significantly lower 2-year NRM rate (14% vs. 49%; P=0.021) and higher 3-year OS rate (63% vs. 29%; P=0.019) compared with myeloablative conditioning; the relapse rate at 2 years was not different between these subgroups. In addition, transplantation from matched related donors was also associated with significantly lower NRM rate (16% vs. 40%; P=0.035) and higher OS rate (63% vs. 24%; P=0.001) compared with transplantation from unrelated donors. Allogeneic SCT appears to be a promising therapeutic strategy in patients with advanced CTCL. Further data from
prospective studies are needed to establish the role of allogeneic SCT in these patients.

Alemtuzumab
Alemtuzumab, a humanized anti-CD52 monoclonal antibody, has shown promising activity in patients with advanced MF and SS.\textsuperscript{116-121} In studies using standard dose alemtuzumab (IV or SC; 30 mg thrice weekly for up to 12 weeks) in heavily pretreated patients with advanced MF or SS, the ORR was 38% to 84% (CR in 0–47%); most patients progressed within 4 to 6 months.\textsuperscript{116,121,122} In a phase II study in patients with advanced MF/SS (N=22; stage III-IV in 86%; median 3 prior therapies), the ORR with single-agent alemtuzumab was 55% (CR in 32%).\textsuperscript{116} The median time to treatment failure (in responding patients) was 12 months. In a recent study of alemtuzumab in heavily pretreated patients with relapsed/refractory erythrodermic MF and SS (N=19), the ORR was 84% (CR in 47%); median PFS and OS was 6 months and 41 months, respectively.\textsuperscript{122} Major toxicities with alemtuzumab included myelotoxicities and infectious complications (including those attributed to cytomegalovirus reactivation), thus prompting the investigation of lower doses of alemtuzumab.\textsuperscript{118,119} In a study of patients with SS (N=14; relapsed/refractory SS, n=11), SC alemtuzumab at low doses (3-15 mg per administration) given for a short time period based on Sézary cell count, was associated with an ORR of 86% (CR in 21%) with an acceptable toxicity profile.\textsuperscript{118} The median time to treatment failure was 12 months. None of the patients who received the 10 mg dose developed hematologic toxicities or infections, which suggested that low-dose alemtuzumab (up to 10 mg per dose) may be a reasonable regimen for patients with pretreated SS.

Management of Relapsed Stage IA-IIB Disease
Clinical trial participation or systemic therapy with agents listed under SYST-CAT A, as single agent or combination therapy, is recommended for patients with stage IA, IB-IIA disease that is progressive or refractory to primary skin-directed therapies (see page MFSS-5). Skin-directed therapy can be used as adjuvant treatment to reduce skin symptoms. Patients who do not respond to treatment with agents under SYST-CAT A should be considered for clinical trial, TSEBT (if not previously administered) or in the absence of a suitable clinical trial, treated with single agent systemic chemotherapy with regimens listed under SYST-CAT B.

In patients with refractory or progressive stage IIB disease with limited-extent tumor disease (with or without patch/plaque), options may include those used as primary treatment for stage IIB generalized extent tumor disease (see page MFSS-6); these options include TSEBT (with or without adjuvant systemic therapy from SYST-CAT-A to improve response duration), systemic chemotherapy, or combination therapies—with or without skin-directed therapies. In patients with stage IIB disease refractory to or progressive with these treatment options, options may include multiagent chemotherapy, consideration for allogeneic SCT or clinical trial participation. Patients are generally treated with multiple agents from SYST-CAT A or SYST-CAT B or with combination therapies before receiving multiagent chemotherapy.

Management of Relapsed Stage III or High-Risk Disease
In patients with refractory or progressive stage III disease, combination therapy or clinical trial should be considered (see page MFSS-7); if the patient remains refractory or progresses during second-line therapy, then clinical trials, systemic therapy with agents listed under SYST-CAT B, or allogeneic SCT (including options using non-ablative conditioning) may be considered. Alemtuzumab may also be considered in this setting. For patients with stage IV/SS or non-Sézary disease with relapse (following a response) or persistent disease (inadequate response), allogeneic SCT may be considered, as appropriate. For
patients with refractory or progressive SS (non-response to primary treatment), systemic therapy with agents listed under SYST-CAT B, alemtuzumab, or clinical trial participation would be appropriate options. For patients with refractory or progressive non-Sézary or visceral disease, clinical trials should be considered.

Considerations for Allogeneic SCT
As mentioned above, allogeneic SCT may be considered for patients with stage IIB-IV disease that is progressive or refractory to primary treatment options. Appropriate patients (stage IIB or stage III MF who have failed multiple systemic therapies/combination therapies and adequate trial of skin-directed therapy; high-risk stage IV patients with relapse or inadequate response following primary treatment with systemic therapies, combination therapies and/or multiagent chemotherapy) may be referred for a transplant consultation. In general, patients should have failed biologic options and single agent chemotherapy prior to allogeneic SCT. When appropriate, TSEBT may be considered as cytoreductive therapy before transplant. Patients with relapsed/progressive disease only in the skin should not be referred for transplant. The ideal timing for allogeneic SCT is when the disease is well controlled with induction therapy and before the disease has progressed to a state where the chance of response or survival with allogeneic SCT is low. This is particularly true for patients with high-risk stage IV disease that has relapsed (or has persistent disease) after primary treatment. For these patients, consideration of allogeneic SCT should be made earlier in the treatment phase to optimize response to induction therapy prior to transplant. Thus, for high-risk stage IV disease, allogeneic SCT should not be a ‘last resort’ option.

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

Supportive Care for Patients with MF/SS
Management of Pruritus
Symptoms of pruritus can be present in a large majority (nearly 90%) of patients with CTCL, and may be associated with decreased quality of life for patients. Patients with MF/SS should be evaluated for pruritus at each visit. Other potential causes of pruritus (e.g., contact dermatitis, atopic dermatitis, psoriasis, other inflammatory skin conditions) should be ruled out. The extent of pruritus should be determined (localized vs. generalized), and potential correlation between disease site and localization of pruritus should be noted. Daily use of moisturizers and emollients are helpful in maintaining and protecting the skin barrier. The treatment of pruritus requires optimizing skin-directed and systemic treatments. Topical steroids (with or without occlusion) can be effective in managing the disease and accompanying pruritus in early-stage disease. First-line options with systemic therapies include antihistamines, the tricyclic antidepressant doxepin or the anticonvulsant gabapentin. In the second-line setting, systemic therapy with the neurokinin-1 receptor antagonist aprepitant, the tetracyclic antidepressant mirtazapine or use of selective serotonin reuptake inhibitors may be considered. Treatment with the oral opioid receptor antagonist naltrexone may be considered if symptoms of pruritus do not resolve with the above agents.

Prevention and Treatment of Infections
Infectious complications are frequent among patients with MF/SS, particularly cutaneous bacterial infections and cutaneous herpes viral infections (e.g., HSV or HZV infections). Bacteremia/sepsis and
bacterial pneumonia were reported as the major cause of death due to infections in a retrospective cohort study of patients with MF/SS. Several preventive measures can be incorporated to minimize infectious complications in patients with MF/SS. These measures include maintaining/protecting the skin barrier (routine use of skin moisturizers and/or emollients), bleach bath or soaks (for limited areas only), avoidance of central lines (particularly for erythrodermic patients) and prophylactic use of mupirocin in cases of *Staphylococcus aureus* (*S. aureus*) colonization. Patients with MF/SS undergoing treatment with alemtuzumab-containing regimens should be closely monitored for cytomegalovirus (CMV) reactivation and preemptively treated with antivirals to avoid overt CMV disease (see Guidelines section for Supportive Care for NHL).

For active or suspected infection in patients with erythroderma, cultures from skin swab and nares (nostrils) should be taken to evaluate for *S. aureus* colonization/infection. Bleach baths or soaks may be helpful if the affected area is limited. Antimicrobial treatments may include intranasal mupirocin and/or oral dicloxacillin or cephalexin. For cases of suspected methicillin-resistant *S. aureus* (MRSA) infection, trimethoprim/sulfamethoxazole (TMP/SMX) or doxycycline should be considered. If no improvements in infection status are observed with the above agents, or if bacteremia is suspected, vancomycin should be initiated. Further information on the appropriate use of vancomycin is included in the NCCN Guidelines for the Prevention and Treatment of Cancer-related Infections (also available at nccn.org).

Infection with Gram-negative rods is common in necrotic tumors, and may lead to serious complications such as bacteremia/sepsis. For active or suspected infections in patients with ulcerated and necrotic tumors, blood cultures should be obtained and empiric therapy with antibacterials should be considered even in the absence of a fever. An antimicrobial agent with broad-spectrum coverage (including coverage for both Gram-negative rods and Gram-positive cocci) should be chosen initially. The role of skin/wound culture is not clear in this setting. Further information on empiric therapy in cancer patients at risk for infections is included in the NCCN Guidelines for the Prevention and Treatment of Cancer-related Infections (at nccn.org).
References


Adult T-Cell Leukemia/Lymphoma

Adult T-cell leukemia/lymphoma (ATLL) is a type of peripheral T-cell malignancy caused by a retrovirus, the human T-cell lymphotropic virus type I (HTLV-1), and is associated with a long period of latency (often manifesting several decades after exposure). ATLL is endemic to several regions, including southwest regions in Japan, the Caribbean, and parts of central Africa, owing to the distribution of HTLV-1. In the International Peripheral T-cell Lymphoma (PTCL) Project, ATLL comprised about 10% of the diagnosis for confirmed cases of PTCL or NK/T-cell lymphomas (N=1,153). ATLL was rare in North America or Europe (≤2%), but prevalent in Asia (25%), with all cases from Asia originating in Japan. Among HTLV-1 carriers in Japan, the cumulative life-time risk of developing ATLL is estimated to be 2.5%; the annual incidence of ATLL in Japan is approximately 700.

ATLL can be associated with an aggressive disease course, with median overall survival (OS) of 6 to 10 months among patients with the acute or lymphoma subtypes. The Lymphoma Study Group of the Japan Clinical Oncology Group (JCOG) have classified ATLL into four subtypes (smoldering, chronic, acute, or lymphoma) based on laboratory evaluations (e.g., serum lactate dehydrogenase [LDH], calcemia, lymphocytosis) and clinical features of ATLL (e.g., lymphadenopathy, hepatosplenomegaly, skin involvement). The smoldering and chronic subtypes are considered indolent forms of ATLL. Both subtypes are usually characterized by 5% or more abnormal T-lymphocytes in the peripheral blood and may have skin or pulmonary lesions (but no ascites or pleural effusion). In addition, the smoldering subtype is associated with a normal lymphocyte count, normal serum calcium level, LDH levels within 1.5 times upper normal limit, and no involvement of liver, spleen, CNS, bone, or gastrointestinal (GI) tract. The expected median OS for this subtype generally exceeds 5 years.

The chronic subtype is characterized by absolute lymphocytosis (≥4 x 10⁹/L) with T-lymphocytes ≥3.5 x 10⁹/L, normal calcium level, LDH levels within 2 times upper normal limit, and no involvement of CNS, bone or GI tract; lymphadenopathy and involvement of liver and spleen may be present. The lymphoma subtype is characterized by absence of lymphocytosis, ≤1% abnormal T-lymphocytes, and histologically-proven lymphadenopathy with or without extranodal lesions. The acute subtype usually presents with leukemic manifestation and tumour lesions, and represent cases that are not classified as any of the other 3 subtypes above. The acute subtype is associated with a rapidly progressive disease course, and features including elevated LDH levels, hypercalcemia (with or without lytic bone lesions), B symptoms, generalized lymphadenopathy, splenomegaly, hepatomegaly, skin involvement, and organ infiltration.

The smoldering and chronic subtypes have a more favorable prognosis compared with the acute or the lymphoma subtypes. In the analysis of patients with ATLL (N=818; mean age 57 years) from the Lymphoma Study Group of JCOG, the estimated 4-year OS rates for patients with acute, lymphoma, chronic, and smoldering subtypes were 5%, 6%, 27%, and 63%, respectively. The median OS was 6, 10, 24 months, and not yet reached, respectively. The maximum duration of follow-up was 7 years in this study. The analysis from the International PTCL Project confirmed the poor outcomes of patients with acute or lymphoma subtypes of ATLL, with a median OS of 10 months. In a recent report from a long-term follow-up of patients with newly diagnosed indolent ATLL (N=90), the median OS was 4 years and the estimated 5-, 10-, and 15-year survival rates were 47%, 25%, and 14%, respectively. In the subgroup analysis, the 15-year OS rate and median OS tended to be higher for the chronic subtype (15% and 5 years,
respectively) than the smoldering subtype (13% and 3 years, respectively). These long-term outcomes appear poorer than expected for patients with indolent ATLL; the heterogeneity in outcomes among patients with even the indolent subtype of the disease may be explained, in part, by differences in patient- and disease-related factors.

In patients with ATLL, poor performance status, elevated LDH level, ≥4 total involved lesions, hypercalcemia and age ≥40 years have been identified as major adverse prognostic factors based on data from a large number of patients. Among patients with the chronic subtype, factors such as poor performance status, ≥4 total involved lesions, bone marrow involvement, elevated LDH, elevated blood urea nitrogen, and low albumin levels have been identified as potential prognostic factors for decreased survival. Further studies with a larger number of patients are needed to elucidate prognostic factors that may help to further risk stratify patients with indolent ATLL. For patients with aggressive subtypes of ATLL, the International PTCL Project recently reported that the International Prognostic Index (IPI) was a useful model for predicting outcomes. Based on univariate analysis, presence of B symptoms, platelet count <150 × 10^9/L, and high IPI score (≥3) were found to be associated with decreased OS. Based on multivariate analysis, however, IPI score was the only independent predictor for OS outcomes. Recently, a report based on data from patients with ATLL in North America (N=89; acute or lymphoma subtypes in 79%) found that IPI scores were not always predictive for ATLL outcomes, and proposed a new prognostic model. In this study, the investigators identified 3 prognostic categories based on the following factors: ECOG performance status, Ann Arbor stage, age, and serum calcium level at diagnosis. Include ATL-PI. http://www.ncbi.nlm.nih.gov/pubmed/22473153.

In the NCCN Guidelines, patients with ATLL are classified into 4 subtypes (chronic, smoldering, acute and lymphoma) according to the Shimoyama criteria.

**Diagnosis**

The diagnosis of ATLL requires histopathology and immunophenotyping of tumor lesion, peripheral blood smear analysis for atypical cells, flow cytometry on peripheral blood and HTLV-1 serology. The presence of ≥5% T-lymphocytes with an abnormal immunophenotype in the peripheral blood is required for the diagnosis of ATLL in patients without histologically proven tumor lesions. The cytological features of ATLL may be broad, but typical ATLL cells are characterized by so-called 'flower cells', which show distinct polylobated nuclei with homogeneous and condensed chromatin, small or absent nucleoli, and agranular and basophilic cytoplasm. These cytological characteristics are most evident in the acute subtype of the disease. HTLV-1 serology should be assessed by ELISA, and if positive, confirmed by western blot. If the result from western blot is indeterminate, then PCR analysis for HTLV-1 can be performed. Monoclonal integration of HTLV-1 proviral DNA occurs in all cases of ATLL; HTLV-1 integration patterns have been reported to have clinical and prognostic implications for ATLL. Bone marrow biopsy or aspiration is generally not required to establish the diagnosis of ATLL. However, bone marrow evaluation may be useful as bone marrow involvement has been reported as an independent predictor of poor prognosis in ATLL. If the diagnosis of ATLL is not established on peripheral blood examination, bone marrow biopsy or biopsy of the lymph nodes or lesions in skin or GI tract should be performed. Biopsy of the suspicious lesion may also help to rule out certain underlying infections (e.g., tuberculosis, histoplasmosis, and toxoplasmosis). Excisional biopsy is recommended instead of core needle biopsy for the lymph nodes.
If a biopsy is performed, the immunophenotyping panel should at minimum include the following markers: CD3, CD4, CD7, CD8, and CD25. The typical immunophenotype in most patients with ATLL involves mature CD4-positive T cells with expression of CD2, CD5, CD25, CD45RO, CD29, T-cell receptor $\alpha\beta$ and HLA-DR. Most ATLL cells lack CD7 and CD26 and have a dim CD3 expression. In the Guidelines, the following is included as representative of a typical immunophenotype for ATLL: CD2+, CD3+, CD4+, CD7-, CD8-, CD25+, CD30-/+, TCR $\alpha\beta$.

The clinical features of ATLL differ by subtype and disease stage, but patients with the most common acute or lymphoma subtypes may frequently present with lymphadenopathy (77%), fatigue (32%), anorexia (26%), skin eruptions (23%), abdominal pain (23%), pulmonary complications (18% due to leukemic infiltration and/or infections), splenomegaly (13%), and hepatomegaly (10%). Bone marrow involvement (28%) and CNS involvement (10%) are also not uncommon.

**Workup**

The initial workup for ATLL should include a comprehensive physical examination with complete skin examination, and CT scans of the chest, abdomen and pelvis. Most patients with acute ATLL have elevated LDH levels, and lymphocytosis is found in patients with the acute or chronic type at presentation. Laboratory evaluations should include a complete blood count (CBC) and metabolic panel (serum electrolyte levels, calcium, creatinine and blood urea nitrogen), and measurement of serum LDH levels.

Upper GI tract endoscopy should be considered in selected cases since GI tract involvement is frequently observed in patients with aggressive ATLL. CNS evaluation using CT scan, MRI and/or lumbar puncture may also be useful for all patients with acute or lymphoma subtypes or in patients with neurological manifestations.

**Response Criteria**

The current response criteria used for ATLL are based on modifications to the original 1991 JCOG response criteria as suggested at the international consensus meeting. The modified response criteria reflect the widely used criteria for CLL and NHL, which were published in 1996 and 1999, respectively. These response criteria are based on the normalization or reduction in the size of enlarged lymph nodes and extranodal masses (as calculated by the sum of the products of the greatest diameters of measurable disease), reduction in the size of spleen or liver and decrease in the involvement of peripheral blood, bone marrow and skin. The response is categorized as a complete remission (CR; defined as complete disappearance of all clinical, microscopic, and radiographic evidence of disease and absolute lymphocyte count, including flower cells, <4 x 10^9/L in the peripheral blood), partial remission (PR; defined as ≥50% reduction in the sum of the products of the greatest diameters of measurable disease without the appearance of new lesions, no increase in spleen or liver size, ≥50% reduction in skin involvement, and ≥50% reduction in absolute lymphocyte counts in peripheral blood), stable disease (SD; failure to achieve CR or PR with no progressive disease) and relapsed disease or progressive disease (PD; new or ≥50% increase in lymph node lesions, extranodal mass, or splenomegaly/hepatomegaly, ≥50% increase in skin involvement, 50% increase from nadir in the count of flower cells and an increase in absolute lymphocyte count, including flower cells, of >4 x 10^9/L). Each of the criterion for the response categories should be observed for a minimal period of 4 weeks to qualify for the response (e.g., CR, PR, SD). The response criteria also includes a category for unconfirmed CR, defined as ≥75% reduction in tumor size but with a
residual mass after treatment, with an absolute lymphocyte count, including flower cells, of <4 x 10^9/L. The usefulness of PET or PET-CT has not been evaluated in the response assessment of patients with ATLL.

**Treatment Options**

The ATLL subtype is an important factor for predicting prognosis and deciding appropriate treatment strategies. Smoldering and chronic subtypes are considered indolent, and are usually managed similarly to indolent NHL with watchful waiting until symptomatic disease. In contrast, the acute and lymphoma subtypes typically require immediate therapy.

A number of small studies and cases have reported on the activity of the combination of an anti-retroviral agent zidovudine and interferon (IFN)-alfa in patients with ATLL. Among patients with primarily treatment-naïve aggressive ATLL, antiviral therapy with zidovudine and IFN-alfa resulted in overall response rate (ORR) of 58%-80% and CR rates of 20%-50%. Outcomes with this therapy for previously treated patients with relapsed/refractory disease were poorer, with ORR 17%-67% (nearly all PRs). The results of a meta-analysis on the use of zidovudine and IFN for patients with ATLL were recently reported by Bazarbachi et al (N=254). Most of the patients (n=207 evaluable) in this analysis had the acute (47%) or lymphoma (41%) subtypes, with the remaining patients presenting with indolent disease. Patients had been treated with first-line antiviral therapy alone (n=75; comprising a combination of zidovudine and IFN-alfa in 97% of cases), chemotherapy alone (n=77; CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone] in 86% of cases) or chemotherapy followed by maintenance antiviral therapy (n=55). Among the patients who received first-line antiviral therapy alone, 60% had the acute subtype; in contrast, among the patients who received chemotherapy alone, 62% had the lymphoma subtype. In patients with available survival data and recorded first-line therapy (n=207), the 5-year OS rates were 46%, 20% and 12%, respectively, for patients who received first-line antiviral therapy alone, chemotherapy alone and chemotherapy followed by antiviral therapy. The ORR was 66% (CR in 35%) among patients who received first-line antiviral therapy (n=62 evaluable) and 88% (CR in 25%) among those who received first-line chemotherapy alone (n=48 evaluable). Among patients who received chemotherapy followed by antiviral therapy (n=14 evaluable), the ORR was 93% (CR in 50%). For all patients with follow-up survival data (n=238), the median OS was 12 months and the 5-year OS rate was 23%. In the subgroup analysis by ATLL subtype, median OS was 6 months, 13 months, and not reached, respectively, in patients with acute, lymphoma and indolent (chronic or smoldering) subtypes; the 5-year OS rate was 15%, 16%, and 76%, respectively. In the subgroup analysis by first-line treatment regimen, antiviral therapy resulted in significantly longer median OS (17 months vs. 12 months) and higher 5-year OS rate (46% vs. 14%) compared with chemotherapy (with or without maintenance antiviral therapy).

Interestingly, only the patients with the acute and indolent subtype benefited significantly from first-line antiviral therapy, whereas patients with the lymphoma subtype had worse survival with antiviral therapy and better outcomes with first-line chemotherapy (with or without maintenance antiviral treatment). Multivariate analysis showed that only the ATLL subtype and type of first-line treatment were significant independent predictors for poorer OS. These data suggest that antiviral therapy with zidovudine and IFN-alfa is effective in patients with leukemic ATLL, but not in the lymphoma subtype. A recent retrospective analysis evaluated outcomes in patients with aggressive ATLL (N=73; 60% had lymphoma subtype) treated with chemotherapy alone (n=39; primarily with CHOP-containing regimens) or combined...
therapy with chemotherapy and antiviral agents (zidovudine and INF-alfa; given concurrent or sequential to chemotherapy or deferred). The median OS among patients with the acute and lymphoma subtypes was 7.5 months and 10 months, respectively. The use of antiviral treatments (at any point on the study) was associated with significant OS benefit for both the subgroups with acute and lymphoma ATLL. Among patients with the lymphoma subtype (n=32), treatment with first-line combination therapy (with chemotherapy and antiviral agents) or chemotherapy with deferred antivirals resulted in significant OS benefits compared with chemotherapy alone.

In patients with ATLL, combination chemotherapy with CHOP has resulted in ORR of 64% to 88% and CR rates of 18% to 25%. Median OS in published reports ranges from about 8 to 12 months. In the aforementioned meta-analysis of data from patients with ATLL treated with first-line therapies, chemotherapy (primarily CHOP) alone resulted in median OS of 10 months and chemotherapy with or without maintenance antiviral therapy resulted in median OS of 12 months. As alluded to earlier in the discussion, patients with the lymphoma subtype appeared to benefit more from first-line therapy with CHOP or CHOP-like chemotherapy (with or without maintenance antivirals) than with antivirals alone. In the subgroup of patients with the lymphoma subtype, OS outcome was significantly improved with first-line chemotherapy (n=72; median OS 16 months; 5-year OS 18%), compared with first-line antiviral treatment alone (n=13; median OS 7 months; 5-year OS 0%; P=0.009). Several prospective studies have evaluated the role of more intensive chemotherapy combination regimens. A phase II multicenter study investigated the activity of CHOP followed by a regimen with etoposide, vindesine, ranimustine, mitoxantrone, and G-CSF in patients with ATLL (N=81). The ORR with this intensive regimen was 74% (CR in 36%) and the median duration of response was 8 months. The median OS for all patients remained rather short, at 8.5 months; the 3-year OS rate was 13.5%. In a small phase II trial conducted by the AIDS Malignancy Consortium in patients with aggressive ATLL (N=19), EPOCH chemotherapy followed by antiretroviral therapy (zidovudine, lamivudine, IFN-alfa up to 1 year) resulted in an ORR of 58% (CR in 10.5%) and a median duration of response of 13 months. Although this regimen appeared to be active in this patient population, viral reactivation during therapy coincided with disease progression, which likely contributed to treatment failure. A phase II trial by JCOG evaluated an intensive multidrug combination chemotherapy regimen comprising VCAP-AMP-VECP [vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP), doxorubicin, ranimustine, and prednisone (AMP), and vindesine, etoposide, carboplatin, and prednisone (VECP)], supported by G-CSF, in patients with aggressive ATLL (N=93). The ORR with this regimen was 81% with a CR in 35.5% of patients. The median OS was 13 months and the estimated 2-year OS rate was 31%. Grade 4 neutropenia (65%) and thrombocytopenia (53%) were frequently observed despite the use of G-CSF. Based on the promising results seen in this study, a randomized phase III trial was conducted by JCOG to evaluate first-line therapy with VCAP-AMP-VECP compared with biweekly CHOP (CHOP-14) in patients with aggressive ATLL (N=118). The CR rate was significantly higher with VCAP-AMP-VECP compared with CHOP-14 (40% vs. 25%; P=0.02) but the 1-year PFS rate (28% vs. 16%) and 3-year OS rate (24% vs. 13%) were not significantly different. Median PFS (7 months vs. 5 months, respectively) and median OS (13 months vs. 11 months, respectively) were not different between treatment arms. VCAP-AMP-VECP regimen was associated with higher incidence of toxicities compared with CHOP-14, including grade 4 neutropenia (98% vs. 83%), grade 4 thrombocytopenia (74% vs. 17%) and grade 3-4 infections (32% vs. 15%). Recently, a very limited
number of ATLL cases have been treated with hyper-CVAD (hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), a regimen more commonly used in the treatment of patients with aggressive B-cell NHL and adult acute lymphoblastic leukemias. Promising outcomes in terms of durable CRs have been reported with this regimen in two cases of ATLL, however, prospective evaluations are needed.

Allogeneic HSCT (using myeloablative or non-myeloablative conditioning) may improve outcomes for some patients with ATLL, with suggestion of a graft-versus-leukemia effect. Studies with allogeneic HSCT (primarily using myeloablative conditioning) have reported promising disease-free and OS outcomes in patients with ATLL, with median leukemia-free survival exceeding 17 months and 3-year OS rate of about 45%. However, the transplant procedure was associated with a high treatment-related mortality (TRM) rate of 40% to 63%. In a multicenter retrospective analysis that evaluated outcomes in patients with aggressive ATLL who received myeloablative allogeneic HSCT (N=40), the median OS for all patients following transplant was about 10 months. Acute graft-versus-host disease (GvHD) developed in 67% of patients. The estimated 3-year relapse-free survival and OS rate was 34% and 45%, respectively. The incidence of TRM was 42.5%, with early TRM (within 6 months of transplant) occurring in 13 patients (32.5%). A large retrospective analysis was conducted in patients with aggressive ATLL who underwent allogeneic HSCT (related or unrelated) (N=386). After a median follow up of 41 months, the 3-year OS rate for this patient cohort was 33%. Overall, the incidence of TRM was 43%, which was mainly due to infectious complications and organ failure. Based on multivariate analysis, patient age (>50 years), male sex, lack of CR at the time of transplant, and the use of unrelated or cord blood were identified as adverse prognostic factors for OS outcomes. In an effort to reduce the high rate of TRM observed with allogeneic HSCT, small prospective studies have been conducted to evaluate the use of reduce-intensity conditioning (RIC) in allogeneic HSCT for patients with ATLL. In a combined analysis from two clinical trials (N=29), the 5-year OS rate with RIC allogeneic HSCT was 34%. The NRM rate was 27.5%; 11 patients died due to disease progression. Ten patients are alive at a median follow up of 82 months following transplant.

A recent retrospective study evaluated the role of myeloablative conditioning and RIC allogeneic HSCT in a large group of patients with ATLL in Japan (N=586). The majority of patients had either acute (57%) or lymphoma (28%) subtypes. Patients who received RIC for HSCT were older than those who received myeloablative conditioning regimens (median age 57 years vs. 49 years). The median OS (survival measured from time of HSCT) was 9.5 months among patients who received myeloablative conditioning, with a 3-year OS of 39%. For patients who received RIC, the median OS was 10 months, with a 3-year OS of 34%. The 3-year cumulative incidence of TRM was 38% with myeloablative conditioning and 33% with RIC. The 3-year cumulative incidence of ATLL-related death was 22.5% and 33%, respectively. Based on multivariate analysis, older age (>55 years), male sex, lack of CR at time of HSCT, poorer performance status (PS ≥1), and unrelated donor HSCT were significant independent factors associated with decreased OS outcomes. Older age (>55 years) was a significant independent factor for poorer OS among patients who received myeloablative conditioning, but not for those who received RIC. In multivariate analysis, significant independent factors for risk of TRM included male sex, poorer performance status (PS ≥1), and unrelated donor HSCT; significant independent factors influencing
risks for ATLL-related death included non-CR at time of HSCT, poor PS (PS ≥2), and RIC.\textsuperscript{40} This analysis suggested that use of myeloablative conditioning or RIC resulted in similar outcomes with allogeneic HSCT, and that HSCT may offer long-term survival in some patients with ATLL. Prospective studies in larger groups of patients are warranted to further evaluate the role of allogeneic HSCT (with myeloablative conditioning or RIC) in the management of ATLL.

Patients with ATLL who relapse after allogeneic HSCT have poor prognosis and very limited treatment options. In a retrospective analysis of patients who progressed or relapsed after first allogeneic HSCT (N=35), donor lymphocyte infusion (DLI) was reported to induce long-term remissions in a few patients.\textsuperscript{41} Most patients in this analysis received withdrawal of immunosuppression as the initial intervention. Among the patients who subsequently received DLI (n=9), the median OS after relapsed/progression was 17 months; the 3-year OS was 33%. Debulking of tumors (with dose-reduced CHOP or RT) prior to DLI seemed to be associated with improved outcomes; response was achieved in 5 of 6 patients who underwent pre-DLI cytoreductive therapy. DLI resulted in remission lasting more than 3 years in 3 of the patients.\textsuperscript{41} Among the patients who did not receive DLI (n=26), the median OS was 4 months and the 3-year OS was 14%. The majority of these patients were treated with chemotherapy regimens following initial withdrawal of immunosuppression.\textsuperscript{41} This analysis showed that induction of graft-versus-ATLL effect via treatments such as DLI may provide long-lasting remission in select patients with relapsed ATLL. However, prospective clinical trials are needed to confirm these findings.

NCCN Recommendations

There are no optimal standard treatment regimens for the management of ATLL. Thus, the NCCN Guidelines panel recommends enrollment in clinical trials as one of the options for all patients with ATLL. Prophylaxis with anti-\textit{Strongyloides} agents and prophylaxis with sulfamethoxazole-trimethoprim to prevent \textit{Pneumocystis jirovecii} pneumonia are recommended for all patients undergoing treatment for ATLL.\textsuperscript{10}

\textbf{Primary Therapy}

For patients with chronic or smoldering ATLL subtypes, observation is a valid option for asymptomatic cases since both of these subtypes are considered indolent diseases. Alternatively, if symptoms are present, these patients can be managed with skin-directed therapies (as recommend for patients with mycosis fungoides or Sézary syndrome within this NCCN Guidelines for NHL) for skin lesions, as appropriate, or with antiviral therapy with combination of zidovudine and IFN-alfa. As previously discussed, enrollment in suitable clinical trials is encouraged, where available.

For patients with acute ATLL, treatment options include participation in clinical trials, antiviral therapy with zidovudine and IFN-alfa, or combination chemotherapy regimens (i.e., CHOP, CHOEP, dose-adjusted EPOCH, or hyper-CVAD; all based on limited data only). For patients with the lymphoma subtype, primary treatment options include participation in clinical trials or combination chemotherapy (as mentioned above for acute ATLL); antiviral therapy alone is not considered effective for this group of patients.\textsuperscript{23} CNS prophylaxis (with intrathecal methotrexate and cytarabine and corticosteroids) is recommended in patients with lymphoma subtype. No optimal treatment has been defined for these patients with aggressive ATLL and efficacy
of long-term treatment is limited. As discussed earlier, allogeneic HSCT may be beneficial in some patients with ATLL.

Outside of a clinical trial, if a patient is not responding or is progressing, on antiviral treatment with zidovudine and IFN-alfa, treatment should be stopped. If there is evidence of clinical benefit, treatment should continue until best response is achieved. The duration of initial therapy is usually 2 months. If life threatening manifestations occur, however, treatment can be discontinued before this period.

The optimal chemotherapy regimen for patients with ATLL is not yet established. The regimens listed in the NCCN Guidelines are based on institutional preferences and include CHOP, CHOEP, dose-adjusted EPOCH or hyper-CVAD.

Mogamulizumab (KW-0761) is a humanized monoclonal antibody approved for the treatment of patients with relapsed or refractory CCR4-positive ATLL in Japan. The approval was based on results of a multicenter phase II study for patients with relapsed, aggressive CCR4-positive ATLL (N=28). The primary endpoint of the trial was ORR; the secondary endpoints included PFS and OS outcomes. Patients were treated with mogamulizumab IV 1 mg/kg once per week for 8 weeks, which was the dose derived from the phase I study. The ORR among evaluable patients (n=26) was 50% (95% CI, 30–70%). The median PFS and OS were approximately 5 months and 14 months, respectively. The most common adverse events included infusion reactions (89%) and skin rashes (63%). Mogamulizumab is an investigational agent in the U.S. and has not been approved for any indication by the FDA. This agent is currently being evaluated in previously treated patients with ATLL in a multicenter open-label randomized study in the U.S. and elsewhere.

Response Assessment and Additional Therapy
For patients with chronic or smoldering ATLL who achieve an initial response (at 2 months following start of treatment; responders include those with a CR, uncertified PR, or PR), continuation of zidovudine and IFN-alfa is recommended. If the patient presents with persistent disease or has disease progression at 2 months from start of treatment (non-responders to initial therapy), options for additional therapy include participation in clinical trials, where available, or combination chemotherapy regimens (i.e., CHOP, EPOCH, or hyper-CVAD) or best supportive care. Allogeneic HSCT should be considered for patients with acute or lymphoma subtype.

For patients with acute or lymphoma ATLL subtypes who achieve an initial response to primary therapy, continuation of the prior therapy or allogeneic HSCT (if donor is available) are appropriate options. Patients with acute ATLL with persistent or progressive disease following primary therapy (non-responders) should be treated in the context of a clinical trial, where possible, best supportive care or an alternate regimen not previously used (under first-line therapy for ATLL, for second-line therapy recommended in the Guidelines for PTCL, or antiviral therapy with zidovudine and IFN). In non-responding patients with lymphoma ATLL subtypes after first-line therapy, options for second-line therapy include treatment in the context of a clinical trial, best supportive care or second-line therapy options based on the recommendations for PTCL. In patients with acute or lymphoma ATLL subtypes who achieve a response to second-therapy, allogeneic HSCT should be considered if a donor is available.


T-cell Prolymphocytic Leukemia

Diagnosis

T-cell prolymphocytic leukemia (T-PLL) is a rare malignancy, comprising approximately 2% of all mature lymphoid malignancies. Clinically, patients frequently present with lymphadenopathy, hepatomegaly, splenomegaly, and elevated WBC counts. Skin lesions can also be present in about 30% of patients.

Morphological examinations of peripheral blood, as well as adequate immunophenotyping by flow cytometry, are essential to establish the diagnosis of T-PLL. Peripheral blood smears show prolymphocytes with round or oval nuclei in about half of the cases, and irregular nuclei (often with convolutions) in the remaining cases; in most cases (about 75%), the typically morphology comprises medium-sized prolymphocytes with agranular basophilic cytoplasm and a single visible nucleolus, while in about 20% to 25% of cases, the cell is small and the nucleolus may not be readily visible. Peripheral blood flow cytometry analysis should include the following markers: TdT, CD1a, CD2, CD3, CD4, CD5, CD7, CD8, CD52, and TCRαβ. Under certain circumstances, immunohistochemistry (IHC) analysis on bone marrow biopsy samples may be useful. In such cases, the IHC panel should include TdT, CD1a, CD2, CD3, CD5, and TCL-1. However, in general, bone marrow biopsy is not essential for establishing a diagnosis of T-PLL. The immunophenotype of T-PLL is consistent with a mature post-thymic T-cell phenotype, with a typical immunophenotype that is TdT-, CD1a-, CD2+, CD5+, and CD7+. CD3 expression may be weak on the cell surface but is usually expressed in the cytoplasm. In 65% of cases, the cells are CD4+/CD8- but cases with CD4+/CD8+ (21%) and CD4-/CD8+ (13%) can also be seen. CD52 is often highly expressed. Diffuse infiltration in the bone marrow is typically observed with T-PLL, but diagnosis is difficult to establish based on bone marrow evaluation alone. Tissue histology is not considered essential to establish the diagnosis. Frequent cytogenetic abnormalities in T-PLL include inversions or translocations involving chromosome 14, most commonly, inv(14)(q11;q32) or t(14;14)(q11;q32), which are associated with the TCL-1 oncogene. Although less frequent, the translocation t(X;14)(q28;q11), associated with the MTCP-1 oncogene, may also occur. Overexpression of TCL-1 and MTCP-1 has been implicated in the pathogenesis of T-PLL. Abnormalities in chromosome 8, mainly trisomy 8q, are also frequently observed. Deletions or mutations to the tumor suppressor gene ATM, which localizes to the chromosome region 11q22-23, have also been detected in patients with T-PLL. This gene is mutated in patients with ataxia telangiectasia, and these patients appear to be predisposed to developing T-cell malignancies, including T-PLL; thus, it is postulated that abnormalities in the ATM gene may also be one of the key events in the pathogenesis of T-PLL. Cytogenetics by conventional karyotyping and/or FISH to detect chromosome 14 abnormalities and trisomy 8 should be performed at the time of diagnostic workup. Under certain circumstances, molecular genetics to detect TCR gene rearrangements, MTCP-1 gene rearrangements, ATM mutations, or TCL-1 overexpression, may be useful.

Workup

The initial workup for T-PLL should comprise a comprehensive medical history and physical examination, including careful evaluation of lymph nodes, spleen, and liver, in addition to a complete skin examination and evaluation of performance status. Laboratory assessments should include standard blood work including CBC with differential, and a comprehensive metabolic panel, as well as
measurements of serum lactate dehydrogenase (LDH). Bone marrow evaluation is generally unnecessary, as evaluation of peripheral blood smears and immunophenotyping are sufficient to establish the diagnosis of T-PLL, as discussed above; however, bone marrow assessments may be useful in some cases. CT scans of the chest, abdomen and pelvis should also be performed at the time of initial workup. PET-CT scans may also be useful in selected cases. If treatment regimens containing anthracyclines or anthracenediones are being considered, a MUGA scan or echocardiogram may be useful, particularly for older patients or for patients with a prior history of cardiac disease. Serology for detection of antibodies against the human T-lymphotropic leukemia virus type 1 (HTLV-1) may be useful, especially to distinguish adult T-cell leukemia/lymphoma from T-PLL (HTLV-1 should be negative in the latter). If serology shows positivity for HTLV-1 by ELISA, a confirmatory Western blot should be performed. Screening for active infections and cytomegalovirus (CMV) serology should be strongly considered prior to initiation of treatment with alemtuzumab-containing regimens.

Treatment Options

In the minority of cases where patients are asymptomatic and have a more indolent course of disease, observation is a reasonable approach until symptoms develop. In most cases of T-PLL, however, patients are symptomatic at the time of presentation. T-PLL is an aggressive malignancy associated with rapid disease progression. In an early study of patients with T-PLL (N=78) treated with alkylating agents, pentostatin, or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), the median overall survival (OS) was only 7.5 months; among the subgroup of patients who responded to pentostatin (n=15), the median OS was 16 months. In a retrospective analysis of patients (both previously untreated and treated) with post-thymic T-cell malignancies treated with pentostatin, the overall response rate (ORR) was 45% and complete response (CR) 9% in the subgroup of patients with T-PLL (n=55). The median duration of response was short, however, at 6 months (range, 3–16 months). The median OS from treatment initiation was 17.5 months for responding patients and 9 months for non-responders.

More recently, treatment with the anti-CD52 monoclonal antibody alemtuzumab has shown high response rates in both previously treated and untreated patients with T-PLL. In a study that primarily included pretreated patients with T-PLL (N=39; previously treated, n=37), intravenous (IV) alemtuzumab resulted in an ORR of 76% (CR in 60%). The median disease-free interval (from end of therapy to relapse) was 7 months. Among the patients who were pretreated (n=37), none had achieved a CR to previous therapy and 61.5% were resistant to prior treatments. The median OS for all patients was 10 months, and was 16 months for patients with a CR. Following alemtuzumab, 11 patients proceeded to hematopoietic stem cell transplant (HSCT; autologous HSCT, n=7; allogeneic HSCT, n=4). Outcomes were similar in a subsequent report, in which IV alemtuzumab induced an ORR of 74% (CR in 60%) in patients with relapsed/refractory T-PLL (n=45); the 4-year OS rate in this patient group was 18%. In a larger study in patients with T-PLL (N=76; previously treated, n=72), treatment with IV alemtuzumab induced an ORR of 51% (CR in 39.5%); among the 4 patients who received alemtuzumab as first-line therapy, 3 achieved a CR. The median time to progression (TTP) for all patients was 4.5 months, and the median OS was 7.5 months. Among the patients who achieved a CR, the median response duration and OS was 9 months and 15 months, respectively. In a recent study that evaluated alemtuzumab in the first-line setting using the IV route or subcutaneous (SC) delivery in
patients with T-PLL, response rates were found to be inferior with the SC route of alemtuzumab.\textsuperscript{13} In the small number of patients who were treated with first-line SC alemtuzumab (n=9), the ORR was 33% with no CRs; moreover, 2 of the patients (22%) died of progression of disease during therapy. In contrast, first-line IV alemtuzumab (n=32) induced an ORR of 91% with CR in 81% of patients. The most common toxicities reported with alemtuzumab in patients with T-PLL included infusion-related reactions, prolonged lymphocytopenia, and infectious events, including opportunistic infections.\textsuperscript{14,15}

Alemtuzumab has also been evaluated as part of combination regimens in patients with T-PLL. In a phase II study that evaluated the combination of alemtuzumab and pentostatin in patients with T-cell malignancies, the subgroup of patients with T-PLL (n=13) showed an ORR of 69%, with a CR in 62% of patients.\textsuperscript{17} The median PFS and OS for this subgroup of patients were 8 months and 10 months, respectively. The study included both patients with previously treated and untreated disease.\textsuperscript{17} In a study conducted by the German CLL Study Group in patients with T-PLL (N=18 evaluable; previously treated, n=6), alemtuzumab was given sequentially (as consolidation therapy) to patients who responded to initial courses of chemotherapy with FCM (fludarabine, cyclophosphamide, mitoxantrone).\textsuperscript{18} Patients with stable disease or progression after 2 courses of FCM were also eligible to received alemtuzumab. Following FCM chemotherapy, 15 patients received consolidation with IV alemtuzumab. The ORR after FCM and after alemtuzumab was 66% and 88%, respectively. The median PFS and OS following FCM with alemtuzumab was 11 months and 19 months, respectively.\textsuperscript{18} In a recent follow-up report from this study (N=25; previously treated, n=9), the ORR after FCM was 68% with a CR in 24%.\textsuperscript{19} After consolidation with alemtuzumab, the ORR increased to 92% with a CR in 48% (intent-to-treat population). The median PFS and OS were 12 months and 17 months, respectively. PFS was shorter among patients with higher TCL-1 expression levels. Among the patients who received consolidation with alemtuzumab (n=21), CMV reactivation occurred in 13 patients (62%); 9 of these cases were clinical relevant CMV infections (43%).\textsuperscript{19} Outcomes with this treatment approach appear promising; however, the high rate of CMV reactivation warrants careful monitoring (and preemptive antiviral therapy upon increasing viral load) to prevent the development of CMV-related complications.

The potential utility of allogeneic hematopoietic stem cell transplant (HSCT) in patients with T-PLL has been reported in a number of individual case studies.\textsuperscript{14,20-23} A retrospective study investigated the role of HSCT (allogeneic or autologous) following treatment with alemtuzumab in patients with T-PLL (N=28), and compared the outcomes to a retrospective cohort of patients who received alemtuzumab alone.\textsuperscript{24} Among the group of patients who received allogeneic HSCT after alemtuzumab (n=13), all patients achieved a CR following HSCT (except one patient who was not evaluable), and 5 were alive in CR at a median of 28 months (range, 25 to 110 months) follow-up from transplant. Four patients had relapsed (at 5, 9, 24, and 31 months from transplant) and died; in addition, 4 patients died in CR, resulting in a treatment-related mortality (TRM) rate of 31%. The median OS (from start of alemtuzumab therapy) for all patients who underwent allogeneic HSCT was 33 months; this appeared more favorable to the median OS of 20 months among patients who did not receive transplant after alemtuzumab.\textsuperscript{24} Retrospective analyses of data from databases have evaluated the role of allogeneic HSCT in T-PLL.\textsuperscript{25-27} In a review of data from the CIBMTR database, which included patients with PLL treated with allogeneic HSCT (N=47; T-PLL, n=21 [45%]; B-PLL or unspecified lineage in the remaining cases), the 1-year PFS and OS rates were 33% and 48%, respectively.\textsuperscript{25} The median OS for these patients was 11 months. For
the subgroup of patients with T-PLL (n=21), the median PFS with allogeneic HSCT was 5 months. The 1-year cumulative incidence of TRM was 28%; the 1-year incidence of relapse or disease progression was 39%. In another study, outcomes of allogeneic HSCT in patients with T-PLL were evaluated based on data from the EBMT database (N=41). The median PFS and OS were 10 months and 12 months, respectively. The 3-year relapse-free survival (RFS) and OS rates were 19% and 21%, respectively. The 3-year TRM and relapse rates were 41% for both endpoints; most relapses (71% of cases) occurred within the first year following transplant. Patients who underwent HSCT in first remission (CR or partial remission [PR]) tended to have a lower relapse rate (2-year rate: 30% vs. 46%) and higher event-free survival rate (2-year rate: 39% vs. 15%) compared with those transplanted with advanced disease. Based upon multivariate analysis, the use of total body irradiation (TBI) conditioning and a shorter interval between diagnosis and transplant were significant independent predictors of longer RFS with allogeneic HSCT. None of the variables evaluated were independent predictors of OS outcomes. In another recent retrospective study, outcomes of allogeneic HSCT in patients with T-PLL were evaluated based on data from a multicenter French registry (N=20; transplanted in CR, n=9). The majority of these patients (85%) had received alemtuzumab prior to HSCT. The CR rate after allogeneic HSCT was 85%. At a median follow-up of 29 months, 10 patients remain alive with 7 patients in CR. TRM occurred in 6 patients (30%), with early TRM in 2 of the patients. Four deaths occurred due to disease progression. The estimated 3-year PFS and OS were 29% and 42%, respectively. The 3-year incidence of TRM was 38%. The incidence of relapse was 51%, with a median time to relapse (post-HSCT) of 14 months. Although the available data are based on retrospective evaluations, allogeneic HSCT may offer the best chance for long-term disease control in a subgroup of patients with T-PLL.

Only limited data have been published on the use of autologous HSCT in patients with T-PLL. In the aforementioned study of alemtuzumab in patients with primarily pretreated T-PLL, a small group of patients (n=7) underwent autologous HSCT after achieving a CR with alemtuzumab therapy. Five of these patients were in first CR at the time of HSCT while 2 patients were in second CR. Among these patients, the median OS from time of transplant was 12 months (range, 5+ to 19 months). Four patients (including the 2 patients transplanted in second CR) relapsed after 5 to 14 months and died due to progressive disease. At the time of the report, 3 patients were alive at 5, 7, and 15 months after transplant. In a more recent update, a retrospective analysis evaluated additional patients with T-PLL who underwent autologous HSCT following treatment with alemtuzumab (n=15). All of these patients achieved a CR following HSCT, and 5 were alive in CR at a median of 81 months (range, 8 to 115 months) follow-up from transplant. Nine patients had relapsed at a median of 15 months (range, 5 to 56 months) from transplant, and died; 1 patient died in CR due to an infection and multi-organ failure (TRM of 7%). The median OS (from start of alemtuzumab therapy) for all patients who underwent autologous HSCT was 52 months, which appeared to compare favorably to that of patients who received alemtuzumab alone (20 months). No statistically significant difference in OS was observed between autologous versus allogeneic HSCT (52 months vs. 33 months). At this time, however, the limited availability of data precludes any definitive conclusions regarding the role of autologous HSCT in the management of T-PLL.
NCCN Recommendations

Given the poor prognosis associated with T-PLL, the NCCN Guidelines panel recommends that patients be managed in a clinical trial for novel therapies. In the absence of suitable clinical trials, regimens containing alemtuzumab are recommended as the initial treatment for patients with symptomatic T-PLL. Based on data showing inferior response rates with the SC route of alemtuzumab,¹³,²⁸ the panel recommends that alemtuzumab be administered via IV delivery. Initial treatment options include single-agent therapy with IV alemtuzumab, or alemtuzumab in combination with pentostatin. Sequential therapy with FCM followed by IV alemtuzumab may also be considered. Given the potential risks for viral reactivation and opportunistic infections (e.g., CMV reactivation/infection, *Pneumocystis jiroveci* pneumonia [PCP]) with alemtuzumab therapy, patients should be given antiviral prophylaxis and prophylactic therapy for PCP (e.g., TMP-SMX). In addition, patients should be routinely monitored for CMV reactivation using quantitative PCR test, and treated with preemptive antiviral therapy, as appropriate (see Guidelines section for Supportive Care for NHL).

In patients who achieve a response (CR or partial response [PR]) following initial therapy, consolidation with allogeneic HSCT is recommended if a donor is available, and if the patient is physically fit enough to undergo the transplant procedure. For patients who relapse following an initial response to therapy, or for those who do not respond to therapy (or have progressive disease during therapy), second-line therapy options include clinical trial participation (preferred) or alternate regimens not used during first-line therapy.
References


Extranodal NK/T-Cell Lymphomas, Nasal Type

Mature NK/T-cell lymphomas are a rare and distinct subtype of NHL. NK/T-cell lymphomas are predominantly extranodal and majority of these are of nasal type. Among the confirmed cases of T-cell or NK-cell lymphomas (N=1,153) from the International T-cell Lymphoma Project, extranodal NK/T-cell lymphomas (ENKL) were identified in 12% of patients (nasal 68%, extranasal 26%, aggressive or unclassifiable 6%). The frequency was higher in Asia than in Western countries (22% vs. 5%). In the U.S., the data from the Surveillance Epidemiology and End Results (SEER) registry database reported an increase in the incidence of ENKL, nasal type, from 1992 through 2005, with an annual percentage change of 11%. The incidences were also found to be higher in men and in people of Asian and Pacific Island descent. According to outcomes from the International T-Cell Lymphoma Project, the 5-year overall survival (OS) rate for all patients with ENKL was 32%, and the median OS was about 8 months.

In the 2008 WHO classification, mature NK-cell neoplasms are classified into 2 subtypes: ENKL, nasal type and aggressive NK-cell leukemia. However, ENKL can have an extranasal presentation. ENKL, nasal type is often localized to the upper aerodigestive tract including the nasal cavity, nasopharynx, paranasal sinuses, tonsils, hypopharynx, and larynx. The most common sites of extranasal involvement or metastatic disease include the skin, testis, and gastrointestinal tract. The most common clinical features of ENKL include nasal obstruction or nasal bleeding due to a mass lesion. Compared with patients with nasal type, a greater proportion of the patients with extranasal disease present with advanced stage disease (68% vs. 27%), mass >5 cm (68% vs. 12%), greater than 2 extranodal sites (55% vs. 16%), elevated LDH levels (60% vs. 45%) and B symptoms (54% vs. 39%). The prognosis of ENKL, nasal type is also better, and was associated with higher 5-year OS rate (42% vs. 9%) and longer median OS (19 months vs. 4 months).

Diagnosis

Histopathological features in most cases of ENKL are characterized by diffuse lymphomatous infiltrates, angiocentricity, angiodestructive growth patterns resulting in tissue ischemia and necrosis, and ulceration of mucosal sites. Lymphoma cells can be variable, but are usually medium sized or a mixture of small and large cells. Necrosis is very common in diagnostic biopsies and may delay diagnosis. Biopsy specimen should include edges of the lesions, to increase the odds of having a viable tissue. It may also be useful to perform multiple nasopharyngeal biopsies even in areas that are not clearly involved.

Histopathology and adequate immunophenotyping are essential to confirm the diagnosis. EBV infection is always present in the case of ENKL, and should be determined by EBV-encoded RNA in situ hybridization (EBER-ISH). For high clinical suspicion of ENKL, the initial immunohistochemistry (IHC) panel should include cytoplasmic CD3ε (cCD3ε), CD56 and EBER-ISH. A negative EBER-ISH result should prompt hematopathology review for an alternative diagnosis. Additional recommended markers for the IHC panel include CD20, CD2, CD4, CD5, CD7, CD8, for T-cell lineage. Under certain circumstances, molecular analysis for TCR gene rearrangements may be useful; clonal TCR rearrangements have been found in about a third of cases with ENKL, nasal type.

The typical immunophenotype for NK-cell ENKL is CD20-, CD2+, cCD3ε+ (surface CD3-), CD4-, CD5-, CD7-/-+, CD8-/-+, CD43+, CD45RO+, CD56+, TCRδβ-, TCRδγ-, EBV-EBER+, and cytotoxic
granule proteins positive (e.g., TIA-1+, granzyme B+). For NK-cell lineage, TCR and immunoglobulin gene represent germline sequences. The typical immunophenotype for T-cell lineage is CD2+, cCD3ε+, surface CD3+, variable CD4/CD5/CD7/CD8, TCRαβ+ or TCRδγ+, EBV-EBER+, and cytotoxic granule proteins positive. For T-cell lineage, clonal rearrangements of TCR genes are observed. Ki-67 expression has been reported to be prognostic in patients with stage I/II ENKL, nasal type. High Ki-67 expression (65% or more) was associated with a shorter OS and disease-free survival (DFS). In multivariate analysis, Ki-67 expression and primary site of involvement were found to be independent prognostic factors for both OS and DFS.

Workup

The initial workup for ENKL should include a physical examination with complete ENT evaluation of nasopharynx involvement (including Waldeyer’s ring), evaluation of testicles and skin. A complete blood count with differential and platelets, comprehensive metabolic panel, measurement of serum uric acid, and lactate dehydrogenase (LDH) levels should be conducted. PET-CT scan and CT scans of chest, abdomen, and pelvis, with contrast of diagnostic quality should be performed. If involved, a dedicated CT scan or MRI of the nasal cavity, hard palate, anterior fossa, and nasopharynx is also essential for initial workup. A MUGA scan or echocardiogram should be performed if treatment with anthracycline or anthracenedione is being considered. Evaluation of bone marrow biopsy and aspirate is recommended. Bone marrow involvement is uncommon at diagnosis and occurs in less than 10% of patients. Morphologically negative biopsies should be evaluated by EBER-ISH, and if positive, should be considered involved. Measurement of EBV-DNA viral load is useful in the diagnosis and possibly in the monitoring of the disease. EBV DNA viral load correlates well with clinical stage, response to therapy and poor survival. EBV DNA 6.1 × 10⁷ copies/mL or more at presentation has been shown to be associated with an inferior disease-free survival.

The International Prognostic Index (IPI) is most commonly used for patients with aggressive lymphomas. However, the use of IPI in patients with ENKL is limited because most patients present with localized disease, rare involvement of bone marrow and the presence of constitutional symptoms even with localized disease. Recently, Lee et al have proposed a prognostic model specifically for patients with ENKL, nasal type, based on a large, retrospective, multicenter study that included 262 patients. Most patients had received anthracycline-based chemotherapy regimens with or without radiotherapy (RT). This model identified 4 risk groups with different survival outcomes based on the presence or absence of 4 prognostic factors (B symptoms, stage of the disease, LDH levels and regional lymph node involvement). Most patients had received anthracycline-based chemotherapy regimens with or without radiotherapy (RT). The 5-year OS rates were 81% and 64%, respectively, for patients with no risk factors (Group 1-low risk) and one risk factor (Group 2-low-intermediate risk). The corresponding survival rates were 34% and 7%, respectively, for patients with 2 risk factors (Group 3-intermediate high risk) and 3 or 4 risk factors (Group 4-high risk). Local tumor invasion, defined as bony invasion and/or perforation or invasion of the skin, has also been associated with a low probability of complete response (CR), reduced disease-free survival (DFS) and a high frequency (65%) of systemic failure in patients with stage I/II disease.

The NCCN Guidelines panel recommends measurement of EBV DNA load and calculation of NK/T-cell prognostic index as part of initial work up.
T-cell Lymphomas

Treatment Options

RT is an important component of initial treatment and RT alone has been effective in achieving favorable CR rates compared to chemotherapy alone in patients with localized ENKL.19-27 RT doses of 54 Gy or more are associated with favorable OS and DFS outcomes; the 5-year OS and DFS rates were 75.5% and 60% respectively, compared with 46% and 33%, respectively, for patients receiving RT doses of less than 54 Gy.26 The benefit of RT was noted in the analysis of the aforementioned International T-cell lymphoma Project, which retrospectively reviewed the clinical outcome of patients with ENKL (N=136).1 More patients with ENKL, nasal type, received RT with or without chemotherapy compared with patients with extranasal ENKL (52% vs. 24%); the remainder of treated patients received chemotherapy alone. In the subgroup of patients with early-stage ENKL, nasal type (n=57), the addition of RT to chemotherapy resulted in significantly improved 3-year OS rate compared with chemotherapy alone (57% vs. 30%).1 In a retrospective review of patients with localized stage I/II ENKL, nasal type (N=105), RT alone resulted in higher CR rates compared with chemotherapy alone (83% vs. 20%); CR rates improved to 81% among patients who received RT following chemotherapy.25 The 5-year OS rates were similar among the patient groups that received RT alone (66%; n=31), RT followed by chemotherapy (77%; n=34) and chemotherapy followed by RT (74%; n=37). Notably, the addition of chemotherapy to RT did not appear to improve OS outcomes in this patient population.25 A recent multicenter retrospective study reported that in patients with ENKL, nasal type (N=36), the use of RT with chemotherapy (either concurrent or sequential) was associated with significantly increased CR rate (90% vs. 33%: P<0.0001) and higher 5-year OS (75% vs. 35%; P=0.041) compared with chemotherapy alone.27

Several studies suggest that concurrent chemoradiation is a feasible and effective treatment for the management of localized ENKL.28,29 In the phase I/II study conducted by the Japanese Clinical Oncology Group (JCOG0211 study), high risk patients with stage I/II nasal disease (N=33; with lymph node involvement, B symptoms and elevated LDH) were treated with concurrent RT (50 Gy) and 3 courses of chemotherapy with dexamethasone, etoposide, ifosfamide, and carboplatin (DeVIC).29 With a median follow-up of 32 months, the 2-year OS was 78% and the CR rate was 77%. Long-term follow up from this study (median follow up 68 months) reported 5-year PFS and OS rates of 67% and 73%, respectively.30 Late toxicities were manageable with few grade 3 or 4 events, which included only one grade 3 event (irregular menstruation) and one grade 4 event (perforation of nasal skin). Similar promising results were reported by a Korean group in a phase II study evaluating concurrent chemoradiotherapy with cisplatin and RT (40–52.8 Gy) followed by three cycles of etoposide, ifosfamide, cisplatin, and dexamethasone (VIPD) in patients with stage I/II nasal ENKL (N=30).28 Nine of the patients were considered to have higher risk based on the NK/T-cell prognostic index (discussed earlier). The CR rate was 73% after initial chemoradiation and increased to 80% after VIPD chemotherapy. The estimated 3-year PFS and OS rates were 85% and 86%, respectively.28 Results from these studies support the use of concurrent chemoradiotherapy for patients with stage I/II disease, particularly those patients with high-risk disease features. Concurrent chemoradiation therapy is also the primary treatment option for patients with advanced stage disease as local RT is an essential adjunct for local disease control.

ENKL lymphoma cells are associated with a high expression of P-glycoprotein leading to multidrug resistance that is likely responsible for the poor response to conventional anthracycline based
Several studies have confirmed the activity of L-asparaginase-based regimens for patients with advanced, relapsed or refractory disease. In a series of patients with refractory and relapsed ENKL, nasal type (N=45) treated with L-asparaginase-based chemotherapy followed by involved-field RT (IFRT), the overall response rate (ORR) was 82% (CR in 55%). Both 3-year and 5-year OS rates were 67%. The activity of L-asparaginase in combination with methotrexate and dexamethasone (AspaMetDex regimen) was evaluated in a phase II intergroup study in patients with refractory or relapsed ENKL (N=19). After 3 cycles, patients with localized disease were treated with consolidative RT, if not received previously; those with disseminated disease received high-dose therapy with peripheral blood stem cell infusion. The ORR and CR rate after 3 cycles of treatment was 78% and 61%, respectively. The median progression-free survival (PFS) and OS was both 1 year; the absence of anti asparaginase antibodies and the disappearance of serum EBV-DNA were significantly associated with a better outcome.

More recently, a phase II study from the NK-cell Tumor Study Group evaluated the safety and efficacy of a new L-asparaginase-based combination chemotherapy regimen named SMILE (steroid = dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide) in patients with newly diagnosed stage IV, and relapsed or refractory ENKL, nasal type (N=38 evaluable; newly diagnosed, n=20). A total of 28 patients (74%) completed the planned treatment in the phase II study, with an ORR and CR rate of 79% and 45%, respectively. The response rates were not different between previously untreated patients and patients with relapsed disease. The 1-year PFS and OS rates were 53% and 55%, respectively. In a separate analysis from this study, EBV-DNA copy number was also shown to be predictive for response after SMILE chemotherapy; the ORR was 88% in patients with less than 10^5 copies/mL EBV-DNA in whole blood, compared with 44% in patients with >10^5 copies/mL. In addition, the incidence of grade 4 non-hematologic toxicity was significantly higher among patients with >10^4 copies/mL of EBV-DNA in plasma (55% vs. 14%). A recent phase II study from the Asia Lymphoma Study Group evaluated the SMILE regimen in patients with newly diagnosed or relapsed/refractory NKTL (N=87; relapsed/refractory, n=44; nasal type, n=60). The ORR was 81% (CR in 66%), with similar response rates between newly diagnosed and relapsed/refractory patients. At a median follow up of 31 months, the 4-year DFS was 64% and the 5-year OS was 50%. These data suggest that L-asparaginase-based regimens represent a reasonable option for patients with advanced, relapsed or refractory disease. Long-term benefit needs to be confirmed in larger randomized clinical trials.

Other recent studies have also evaluated the efficacy and safety of L-asparaginase-based regimens following by RT in previously untreated patients with NKTL, nasal type. In a phase II study that evaluated a regimen with 2 or 3 cycles of LVP (L-asparaginase, vincristine and prednisone) combined with RT in newly diagnosed patients with NKTL (N=26), the ORR was 88.5% (CR in 81%); at a median follow up of 27 months, the 2-year PFS and OS rates were 81% and 88.5%, respectively. Grade 3 leukocytopenia occurred in 2 patients (8%), and no grade 4 toxicities or treatment-related deaths were reported. In another phase II study, a regimen with GELOX (gemcitabine, oxaliplatin, and L-asparaginase) followed by IFRT was evaluated in newly diagnosed patients with stage IE/IIE NKTL (N=27). The ORR with this regimen was 96% (CR in 74%), and the 2-year PFS and OS rates were both 86%. Grade 3 or 4 toxicities were infrequent, and no treatment-related deaths were reported. Outcomes from these studies will need to be confirmed in larger prospective studies.
High-dose therapy with autologous stem cell rescue (HDT/ASCR) has been evaluated as a consolidation therapy for patients with early and advanced-stage disease responding to primary therapy. In retrospective analyses, disease status at the time of HDT/ASCR was the most important prognostic factor for survival and relapse-free survival.41-43 A retrospective analysis in patients who underwent HDT/ASCR (N=47) showed that among patients with CR at the time of HDT/ASCR, 5-year disease-specific survival rates were significantly higher in the transplant group compared with the historical non-transplant control group (87% and 68% respectively).43 When stratified by risk based on NK/T-cell prognostic index, there was no significant difference in disease-specific survival rates between the transplant and control groups for patients with low risk (87% vs. 69%), whereas among patients in the high-risk group, the survival benefit with transplant was significantly greater (100% vs. 52%).43 In a retrospective study by the NK-cell Tumor Study Group, a subgroup of patients with ENKL, nasal type, underwent HDT/ASCR (n=15).44 Among these patients, 7 were alive in CR at a median 48+ months after transplant (range, 25+ to 87+ months); 6 patients died due to the disease, all within 5 months from transplant (range, 0.2 to 5 months). Most of the patients who were alive in CR had a first or second CR at the time of the transplant.44 In a recent retrospective analysis from the Lymphoma Working Group of the Japan Society for Hematopoietic Cell Transplantation (JSHCT), outcomes were compared between treatment with autologous (n=60) versus allogeneic (n=74) hematopoietic stem cell transplantation (HSCT) in patients with ENKL.45 A greater proportion of patients had stage IV disease in the allogeneic compared with the autologous HSCT group (64% vs. 33%), and a smaller proportion in the allogeneic HSCT group had low-risk IPI scores (34% vs. 62%). Thus, patients who underwent autologous HSCT in this series appeared to have better prognostic features. The 2-year OS rate was significantly higher with autologous compared with allogeneic HSCT (69% vs. 41%). However, the type of transplant was not a significant prognostic factor in multivariate analysis, and when controlling for other factors that were significant (i.e., stage IV disease, non-CR and performance status at transplant).45

Allogeneic HSCT has also been evaluated in the management of ENKL in several retrospective patient series and case reports.44,46-49 In a retrospective, questionnaire-based study of patients with NK-cell malignancies (N=28; ENKL, n=22), chemosensitive and refractory patients underwent allogeneic HSCT with primarily myeloablative regimens.48 The 2-year PFS and OS rates in this series were 34% and 40%, respectively. Several small case reports have suggested favorable long-term outcomes for patients with relapsed/refractory ENKL who received allogeneic HSCT, with patients achieving continuous remission for 3 to 5 years.47,49 In a retrospective study by the NK-cell Tumor Study Group, a small subgroup of patients with ENKL, nasal type, underwent allogeneic HSCT (n=5).44 Two patients were alive in CR at 56+ months and 78+ months after transplant; 1 patient died due to the disease 2 months from transplant, and 2 patients died in CR.44

**NCCN Recommendations**

Because ENKL are rare malignancies, randomized trials comparing different regimens have not been conducted to date. Therefore, standard therapy has not yet been established for patients with ENKL. Most of the available data are from retrospective analyses and small prospective series. It is recommended that patients with ENKL are treated at centers with expertise in the management of this disease and when possible, enrolled on clinical trials.

**Induction Therapy**

In the NCCN Guidelines, patients with ENKL are stratified by nasal versus extranasal disease at presentation and then by the stage of the disease.
Patients with stage I disease are further stratified based on risk factors (age ≥60 years, presence of B symptoms, ECOG performance status ≥ 2 or more, regional lymph node involvement, local tumor invasion elevated LDH, histological evidence of high Ki-67 staining and EBV DNA ≥6.1 x 10^7 copies/mL).

Participation in a clinical trial is the preferred option for all patients with ENKL with any stage disease. Selected patients with stage I nasal disease without risk factors can be treated with RT (≥50 Gy) alone. Alternatively, patients with stage I nasal ENKL can be treated similarly to patients with stage I disease with risk factors or to those with stage II disease, with concurrent chemoradiation therapy [RT (50 Gy) and 3 courses of DeVic or RT (40–52.8 Gy) and cisplatin followed by 3 cycles of VIPD] or sequential chemoradiation [SMILE followed by RT (45–50.4 Gy) or VIPD followed by RT (45–50.4 Gy)]. Patients with stage IV nasal ENKL and patients with extranasal disease (any stage) can be treated with L-asparaginase-based combination chemotherapy (AspaMetDex or SMILE regimen) with or without RT, or concurrent chemoradiation therapy [RT (50 Gy) and 3 courses of DeVic or concurrent RT(40-52.8 Gy) and cisplatin followed by 3 cycles of VIPD]. Note that pegaspargase should be used in place of L-asparaginase, as the latter is no longer commercially available in the U.S.

**Response Assessment and Additional Therapy**

Patients are restaged after induction therapy. Restaging should include appropriate imaging studies (CT, MRI or PET-CT) based on the type of study performed at the initial work up, endoscopy with visual inspection, repeat biopsies and measurement of EBV DNA. It should be noted, however, that the role of PET scan is not well established in this disease.

Patients with stage I nasal disease achieving a CR to induction therapy may be observed without further treatment. A CR in this case should also include a negative ENT evaluation. For patients with a PR after induction, HSCT is a reasonable option; if a donor is available, an allogeneic HSCT is the preferred option. If eligible, HSCT should also be considered for all patients with stage II or IV nasal disease and extranasal disease (any stage) achieving a CR or PR to induction therapy.

For patients with refractory ENKL (nasal or extranasal, and regardless of disease stage), L-asparaginase-based combination chemotherapy (using pegaspargase in place of L-asparaginase), as described for induction therapy, may offer benefit. Only limited data exist regarding the role of HSCT in this patient population. Salvage chemotherapy (with L-asparaginase-based combination therapy, using pegaspargase) or best supportive care is the recommended option for all patients with refractory disease.
References


