National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

T-Cell Lymphomas

Version 3.2018 — February 22, 2018

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NCCN Guidelines Version 3.2018 Panel Members
T-Cell Lymphomas

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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 indicated.

See NCCN Categories of Evidence and Consensus.

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NCCN Guidelines Version 3.2018 Updates T-Cell Lymphomas

Updates in Version 3.2018 of the NCCN Guidelines for T-Cell Lymphomas from Version 2.2018 include:

Mycosis Fungoides/Sezary Syndrome

MFSS-A

- **Skin-directed therapies, Local radiation was clarified from "8–36 Gy" to "(8-12 Gy; 24-30 Gy for unilesional presentation).” Also for MFSS-C.**

MS-1

- **The discussion section was updated for the following subtypes to reflect the changes in the algorithm.**
  - **Mycosis Fungoides/Sezary Syndrome (MFSS)**
  - **Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders (PCTLD)**
  - **Adult T-Cell Leukemia/Lymphoma (ATLL)**
  - **T-Cell Prolymphocytic Leukemia (TPLL)**

Updates in Version 2.2018 of the NCCN Guidelines for T-Cell Lymphomas from Version 1.2018 include:

MS-1

- **The discussion section for Extranodal NK/T-Cell Lymphoma, nasal type was updated to reflect the changes in the algorithm.**

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NCCN Guidelines Version 3.2018 Updates
T-Cell Lymphomas

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Updates in Version 1.2018 of the NCCN Guidelines for T-Cell Lymphomas from Version 3.2017 include:

Global changes

- Suggested treatment regimen references were updated throughout the guidelines.
- Diagnosis,
  - Essential, bullet for "Adequate immunophenotyping to establish diagnosis" was revised.
    - ◊ IHC panel *may include*...
    - ◊ Cell surface marker analysis by flow cytometry *may include*...
  - Useful Under Certain Circumstances
    - ◊ Bullet was revised, "Assessment of HTLV-1 by serology or other methods in at-risk populations. ~~HTLV-1 PCR if serology is indeterminate.~~"

Peripheral T-Cell Lymphomas

TCEL-1

- Diagnosis, Essential
  - 2nd bullet, "An FNA alone is not sufficient for the initial diagnosis of peripheral" was replaced with "Excisional or incisional biopsy is preferred over needle biopsy. An FNA biopsy alone is not sufficient for the initial diagnosis of lymphoma. A core needle biopsy is not optimal but can be used under certain circumstances. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques may be sufficient for diagnosis."
  - 3rd bullet, 1st sub-bullet was revised, "IHC panel *may include* CD20, CD3, CD10, BCL6, Ki-67, CD5, CD30, CD2, CD4, CD8, CD7, CD56, ~~CD57~~, CD21, CD23, EBER-ISH, *TCRbeta, TCRdelta*, *PD1/CD279*, ALK"
- Diagnosis, Useful Under Certain Circumstances
  - 1st bullet, "Molecular analysis to detect ~~antigen receptor gene rearrangements~~ *clonal T-cell antigen receptor (TCR) gene rearrangements or other assessment of clonality;* t(2;5) and variants" and footnote c was added, "Such as FISH, karyotype, genomic analysis."
  - 2nd bullet was revised: "*Consider molecular analysis to detect* DUSP22 rearrangement if ALCL, ALK negative"
  - 3rd bullet was revised, "Additional immunohistochemical studies to ~~establish lymphoma subtype~~ *characterize subsets of PTCL (eg, T-follicular helper [TFH] cell origin)*: ßF1, ~~TCR-CγM1, PD1/CD279~~, CXCL13, *ICOS, BCL6, TCRdelta, cytotoxic T-cell markers*."
- Subtypes
  - "Nodal peripheral T-cell lymphoma with TFH phenotype" and "Follicular T-cell lymphoma" were added. (Also for other TCEL pages)

TCEL-2

- Workup, Essential
  - 5th bullet was revised, "Bone marrow biopsy ± *aspirate*"
  - 9th bullet was revised, "~~Abdominal/pelvic (C/A/P) CT with contrast of diagnostic quality and/or~~ PET/CT scan *and/or chest/abdominal/pelvic (C/A/P) CT with contrast of diagnostic quality*"
- Workup, Useful in Selected Cases
  - The following bullets were added:
    - ◊ Hepatitis B testing
    - ◊ Consider quantitative EBV PCR
    - ◊ Consider celiac disease in newly diagnosed EATL

TCEL-3

- ALCL, ALK positive, Stage I, II
  - First-line therapy, "Multiagent chemotherapy x 3–4 cycles + ISRT (30–40 Gy)" was changed from a category 2A to a category 2B.
  - After first-line therapy, "Interim restaging with PET/CT or C/A/P CT scan with contrast" was added and the options for "Complete or partial response" and "Progressive or refractory disease" were added.
- Footnote j was added, "Consider consolidative HDT/ASCR for high-risk IPI patients in CR1."

TCEL-4

- "Nodal PTCL, TFH" and "FTCL" were added.
- After first-line, "Interim restaging with PET/CT or C/A/P CT scan with contrast" was added and the options for "Responding disease" and "Progressive or refractory disease" were added.
- Footnote o was added, "If PET/CT scan positive, rebiopsy before changing course of treatment."

TCEL-5

- Relapsed/refractory disease, no intention to transplant,
  - "and/or Best supportive care" was added as an option.
  - After second-line therapy, see Suggested Regimens, options for "complete or partial response" and "no response" were added.

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Updates in Version 1.2018 of the NCCN Guidelines for T-Cell Lymphomas from Version 3.2017 include:

TCEL-A

- Two new prognostic indices were added
  - Prognostic Index for PTCL-U (modified-PIT)
  - International T-cell Lymphoma Project

TCEL-B 1 of 5

- First-line therapy
  - ALCL, ALK+ histology
    - ◊ "CHOP-21" was changed to "CHOP"
    - ◊ Dose-adjusted EPOCH was added.
  - Other histologies
    - ◊ Footnote c was added, "Other histologies include ALCL, ALK-; PTCL, NOS; AITL; EATL; MEITL; Nodal PTCL, TFH; FTCL." Also for TCEL-B 2 of 5.
    - ◊ Preferred regimens, "CHOP-14" and "CHOP-21" was changed to "CHOP"
    - ◊ Other recommended regimens, HyperCVAD was changed from a category 2A to a category 3 recommendation.

TCEL-B 2 of 5

- Second-line and Subsequent Therapy for PTCL-NOS and Other Histologies
  - The following footnotes were added,
    - ◊ Interpretation of CD30 expression is not standardized. Responses have been seen in patients with a low level of CD30-positivity. (Also for TCEL-B 3 of 5)
    - ◊ While alemtuzumab is no longer commercially available, it may be obtained for clinical use. (Also for TCEL-B 3 of 5)

TCEL-B 4 of 5

- Second-line and Subsequent Therapy for ALCL
  - "Brentuximab vedotin" was added as the "preferred regimen" for both with intention and no intention to transplant.
  - "Crizotinib (ALK+ ALCL only)" was added as an other recommended single agent for both with intention and no intention to transplant.

Breast Implant-Associated ALCL

BIAA-1

- After initial workup, if ultrasound inconclusive, "if not previously done" was added to breast MRI and the algorithm was directed back to initial workup.
- Pathologic workup
  - 2nd bullet, Essential for diagnosis of BIA-ALCL
    - ◊ Sub-bullet was revised, "IHC and flow cytometry for T~~-cell markers and CD30~~ *CD2, CD3, CD4, CD5, CD7, CD8, CD30, CD45, and ALK*."
- The following footnotes were added,
  - Larger volume of fluid yields a more accurate diagnosis.
  - Breast implant-associated ALCL (BIA-ALCL) is usually ALK-negative but has a good prognosis.

BIAA-2

- Extended disease, dose for RT was added, "24–36 Gy."
- Footnotes
  - Footnote f was added, "See Proposed TNM Staging for Breast Implant–Associated Anaplastic Large-Cell Lymphoma (BIAA-B)."
  - Footnote g was revised, "For BIA-ALCL, bone marrow biopsy is only needed in selected cases *(eg, extensive disease or unexplained cytopenia)*."

BIAA-B

- The "*Proposed* TNM Staging for Breast Implant–Associated Anaplastic Large-Cell Lymphoma" was added to the algorithm.

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Updates in Version 1.2018 of the NCCN Guidelines for T-Cell Lymphomas from Version 3.2017 include:

Mycosis Fungoides/Sezary Syndrome

MFSS-1

- Diagnosis, Essential
  - "Molecular analysis to detect clonal T-cell antigen receptor (TCR) gene rearrangements or other assessment of clonality" was moved from Useful to Essential and footnote f was added, "Such as FISH, karyotype, genomic analysis."
- Diagnosis, Useful
  - 1st bullet was revised, "Assessment of peripheral blood for Sezary cells (~~in cases where~~ *in extensive skin disease where* skin *biopsy* is not diagnostic, ~~especially T4~~ *and/or strongly of advanced-stage disease*) including"
  - 2nd bullet, "*Core needle* biopsy *(FNA is often inadequate)* of suspicious lymph nodes (~~in absence of definitive skin diagnosis~~ *if biopsy of skin is not diagnostic*)."
- Footnotes
  - Footnote b was revised, "Clinically *suspicious and* ~~or~~ histologically non-diagnostic cases."
  - Footnote e was revised by adding, "A negative PCR in the setting of high clinical suspicion does not exclude the diagnosis of MF."

MFSS-2

- Workup, Essential
  - Imaging studies, 1st sub-bullet was revised by adding, "consider for T2a (patch disease with ≥10% BSA)."
  - "Pregnancy testing in women of child-bearing age" was moved from Essential to Useful and revised by adding, "if contemplating treatments that are contraindicated in pregnancy."
- Workup, Useful
  - 2nd bullet was revised, "*Core needle* biopsy (FNA is often inadequate)..."

MFSS-5

- Footnote u was added, "See Principles of Radiation Therapy For MF/SS. (MFSS-C)." Also added for the other MFSS pages as appropriate.

MFSS-6

- Stage IB-IIA,
  - For CR/PR or inadequate response, if relapse with or persistent T1-T2 disease, "± adjuvant local skin treatment" was added to "T2: (see generalized skin treatment) (MFSS-A)."

MFSS-9

- Sezary syndrome
  - For CR/PR or inadequate response, under relapse or persistent disease, "Clinical trial; consider allogeneic transplant, as appropriate; and alemtuzumab" were removed.
  - For Refractory disease to multiple previous therapies or progression, "Consider allogeneic HCT, as appropriate" was added.
- Non-Sezary or visceral disease
  - For Refractory disease to multiple previous therapies or progression, "Consider allogeneic HCT, as appropriate" was added.

MFSS-A 1 of 4

- Systemic therapies
  - ◊ Brentuximab vedotin was added to Category A as a category 2A recommendation.
  - ◊ Footnote h was added, "A randomized phase 3 trial comparing brentuximab vedotin (BV) with physician's choice of oral bexarotene or methotrexate, showed superior clinical outcome of BV in patients with CD30+ MF and pcALCL. CD30 positivity was defined as CD30 expression >10% of total lymphoid cells in at least 1 of minimal 2 skin biopsies required to evaluate for eligibility. Forty-four percent of eligible patients with MF had at least 1 screening skin biopsy with CD30 <10%. In the two previously reported investigator-initiated studies, clinical responses with BV was observed across all CD30 expression levels including in those with negligible CD30 expression."

MFSS-C

- "Principles of Radiation Therapy for MF/SS" was added to the algorithm.

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Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders

PCTLD-2

- Diagnosis, Essential
  - 4th bullet, sub-bullet was removed "Histopathology review of adequate biopsy (punch, incisional, or excisional)" and added to second sub-bullet, "Biopsy of all types *(punch, incisional, or excisional)* of clinical lesions..."
  - 5th bullet, first sub-bullet was revised by removing, "ßF1."
- Diagnosis, Useful under certain circumstances
  - 1st bullet, Expanded IHC, "FISH 6p25.3" was removed.
  - 2nd bullet was revised, "Molecular analysis to detect ~~antigen receptor gene rearrangements~~ *clonal T-cell antigen receptor (TCR) gene rearrangements (TCRbeta, TCR gamma) or other assessment of clonality"* and footnote j was added, "Such as FISH, karyotype, genomic analysis."
  - 3rd bullet was added, "FISH: DUSP22 gene rearrangement."

PCTLD-4

- Primary cutaneous ALCL, multifocal lesions
  - The primary treatment recommendations were separated into "preferred" and "other"
    - ◊ Brentuximab vedotin was listed as "preferred" and was changed from a category 2A to a category 1 recommendation.
    - ◊ The remaining primary treatment options are listed under "other recommended regimen."
  - After No response/refractory disease, the algorithm was redirected to "See Multifocal lesions below."
- Cutaneous ALCL with regional node
  - The primary treatment recommendations were separated into "preferred" and "other recommended regimen"
    - ◊ Brentuximab vedotin ± ISRT was listed as "preferred."
    - ◊ The remaining primary treatment options are listed under "other."

PCTLD-5

- LyP
  - Limited lesions or asymptomatic was separated by "Limited lesions, asymptomatic" and "Limited lesions, symptomatic."
  - After primary treatment, "asymptomatic disease" was changed to "response" and "symptomatic disease" was changed to "No response/ refractory disease."
    - ◊ For relapsed/refractory disease after response, "continue observation" was changed to "Continue current management" and "topical steroids" was removed.
    - ◊ For relapsed/refractory disease after no response/refractory disease, "clinical trial" was added.

PCTLD-5

- LyP
  - "Or symptomatic" was removed from extensive lesions.
    - ◊ For relapsed/refractory disease after response, the 3rd option was revised, "Retreat *with primary treatment* or treat with alternative regimen not used for primary treatment."
    - ◊ For relapsed/refractory disease after no response/refractory disease, the algorithm was redirected to "Clinical trial or Treat with alternative regimen not used for primary treatment."

T-Cell Large Granular Lymphocytic Leukemia

LGLL-1

- Diagnosis, Essential
  - 2nd bullet, "Flow cytometry on peripheral blood" was added.
  - "Bone marrow aspirate and biopsy" was moved from Essential to Useful.
- Diagnosis, Useful
  - 3rd bullet was revised, "Molecular analysis to detect *clonal* T-cell antigen receptor (TCR) gene rearrangements *or other assessment of clonality* ~~TCRß, TCRγ~~" and footnote g was added, "Such as FISH, karyotype, genomic analysis."
- Workup, Essential
  - 6th bullet was revised, "Serologic studies: HIV-1,2; HTLV-1,2 *for at-risk populations*."
- Footnote a was added, "Approximately 10% of LGLL will be of the NK, provisional type called chronic lymphoproliferative disorder of NK-cells. This is treated with a similar approach to T-LGL."

Adult T-Cell Leukemia/Lymphoma

ATLL-1

- Workup
  - Essential, 2nd bullet, "Electrolytes, BUN, creatinine, serum calcium, serum LDH" was changed to "Comprehensive metabolic panel" and "LDH" was added as a separate bullet.
  - Useful, 6th bullet was added, "Uric acid."

ATLL-2

- Footnote i was revised, "~~Supportive care: anti-infectious prophylaxis with sulfamethoxazole/trimethoprim + strongyloidosis is recommended.~~ Anti-infective prophylaxis: Pneumocystis jirovecii pneumonia (PJP) prophylaxis with sulfamethoxazole/trimethoprim or equivalent; Screening and treatment (if needed) for strongyloidiasis."

ATLL-3

- Footnote p was revised, "CNS prophylaxis: ~~intrathecal chemotherapy~~ is *strongly* recommended ~~(methotrexate and cytarabine and corticosteroids)~~."

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Updates in Version 1.2018 of the NCCN Guidelines for T-Cell Lymphomas from Version 3.2017 include:

T-Cell Prolymphocytic Leukemia

TPLL-1

- Diagnosis, Essential
  - 1st bullet was revised, "Molecular analysis to detect *clonal* T-cell antigen receptor (TCR) gene rearrangements *or other assessment of clonality* ~~(TCRß, TCR); MTCP1 gene rearrangement~~; ~~ATM mutation~~" and footnote c was added, "Such as FISH, karyotype, genomic analysis."
- Workup, Essential
  - 3rd bullet, "electrolytes, BUN, creatinine" was separated from LDH and added as "Comprehensive metabolic panel."

TPLL-2

- Primary Treatment
  - 2nd bullet, "preferred" was added to "intravenous alemtuzumab alone."
  - 3rd bullet, "Alemtuzumab-containing regimens" was changed to "Other regimens"
    - ◊ "In selected patients" was added to "FMC followed by IV alemtuzumab" and "IV alemtuzumab and pentostatin."
  - Footnote h was added, "While alemtuzumab is no longer commercially available, it may be obtained for clinical use."
- Consolidation after CR or PR was revised, "Consider allogeneic *hematopoietic* cell transplant ~~(if donor available)~~" and footnote i was added, "Consider HDT/ASCR if a suitable donor is not available."

Extranodal NK/T-Cell Lymphoma, nasal type

NKTL-1

- Diagnosis, Useful
  - 1st bullet was revised, "Molecular analysis to *clonal* T-cell antigen receptor (TCR) gene rearrangements *or other assessment of clonality*" and footnote g was added, "Such as FISH, karyotype, genomic analysis."

NKTL-2

- Workup, Essential
  - 2nd bullet, "ENT evaluation of nasopharynx" was added.
  - 14th bullet was revised, "EBV viral load *by quantitative PCR*."

NKTL-3

- Stage I,II
  - For fit for chemotherapy, the last induction therapy option was revised, "Sandwich chemoradiation ~~in selected patients.~~"

NKTL-4

- Nasal, for both Stage I,II and Stage IV, the following revisions were made
  - "Refractory disease" was changed to "No response"
  - Additional therapy, "Second-line chemotherapy" was clarified as "combination chemotherapy regimen (asparaginase-based)"
  - After combination chemotherapy regimen, two options for "Relapsed/Refractory Therapy" were added to "HCT, if eligible"
    - ◊ Clinical trial (preferred)
    - ◊ Pembrolizumab
    - ◊ Footnote q was added, "Clinical trial is the preferred relapsed/refractory option. In the absence of a clinical trial, pembrolizumab is an appropriate option."
- Footnote o was added, "May include H&P, ENT evaluation, PET/CT scan, EBV viral load by quantitative PCR."
- Footnote r was revised, "Allogeneic preferred, if ~~matched~~ donor available."

NKTL-B 1 of 2

- New footnotes were added,
  - See Asparaginase Toxicity Management in the NCCN Guidelines for Acute Lymphoblastic Leukemia.

Supportive Care

LYMP-A 1 of 2

- Tumor Lysis Syndrome
  - Laboratory hallmarks of TLS, "elevated creatinine" was added.

LYMP-A 2 of 2

- Anti-CD52 Antibody Therapy: Alemtuzumab, three bullets were added:
  - Herpes virus prophylaxis with acyclovir or equivalent
  - PJP prophylaxis with sulfamethoxazole/trimethoprim or equivalent
  - Consider antifungal prophylaxis

Principles of Radiation Therapy

LYMP-C 3 of 4

- General Dose Guidelines, "RT in conventional fraction sizes" was added to the heading.
- 3rd bullet, dosing for primary cutaneous anaplastic large cell lymphoma was revised from "30–36 Gy" to "24–36 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.**
- **Excisional or incisional biopsy is preferred over core needle biopsy. An FNA biopsy alone is not sufficient for the initial diagnosis of lymphoma. A core needle biopsy is not optimal but can be used under certain circumstances. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core needle biopsy and FNA biopsy in conjunction with appropriate ancillary techniques may be sufficient for diagnosis.**
- **Adequate immunophenotyping to establish diagnosis[a]**
  - **IHC panel may include CD20, CD3, CD10, BCL6, Ki-67, CD5, CD30, CD2, CD4, CD8, CD7, CD56, CD21, CD23, EBER-ISH, TCRbeta, TCRdelta, PD1/CD279, ALK with or without**
  - **Cell surface marker analysis by flow cytometry may include kappa/lambda, CD45, CD3, CD5, CD19, CD10, CD20, CD30, CD4, CD8, CD7, CD2; TCRalpha, TCRbeta, TCRgamma**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **Molecular analysis to detect[b] clonal T-cell antigen receptor (TCR) gene rearrangements or other assessment of clonality;[c] t(2;5) and variants**
- **Consider molecular analysis to detect *DUSP22* rearrangement if ALCL, ALK negative**
- **Additional immunohistochemical studies to characterize subsets of PTCL (eg, T-follicular helper [TFH] cell origin): ßF1, CXCL13, ICOS, BCL6, TCRdelta, cytotoxic T-cell markers**
- **Karyotype to establish clonality**
- **Assessment of HTLV-1[d] by serology or other methods in at-risk populations.**

SUBTYPES

Subtypes included:[e]

- **Peripheral T-cell lymphoma (PTCL), NOS**
- **Angioimmunoblastic T-cell lymphoma (AITL)[f]**
- **Anaplastic large cell lymphoma (ALCL), ALK positive**
- **ALCL, ALK negative**
- **Enteropathy-associated T-cell lymphoma (EATL)**
- **Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)[g]**
- ***Nodal peripheral T-cell lymphoma with TFH phenotype (PTCL,TFH)***
- ***Follicular T-cell lymphoma (FTCL)***

→ **See Workup (TCEL-2)**

Subtypes *not* included:

- **Primary cutaneous ALCL (See PCTLD-1)**
- **All other T-cell lymphomas**

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

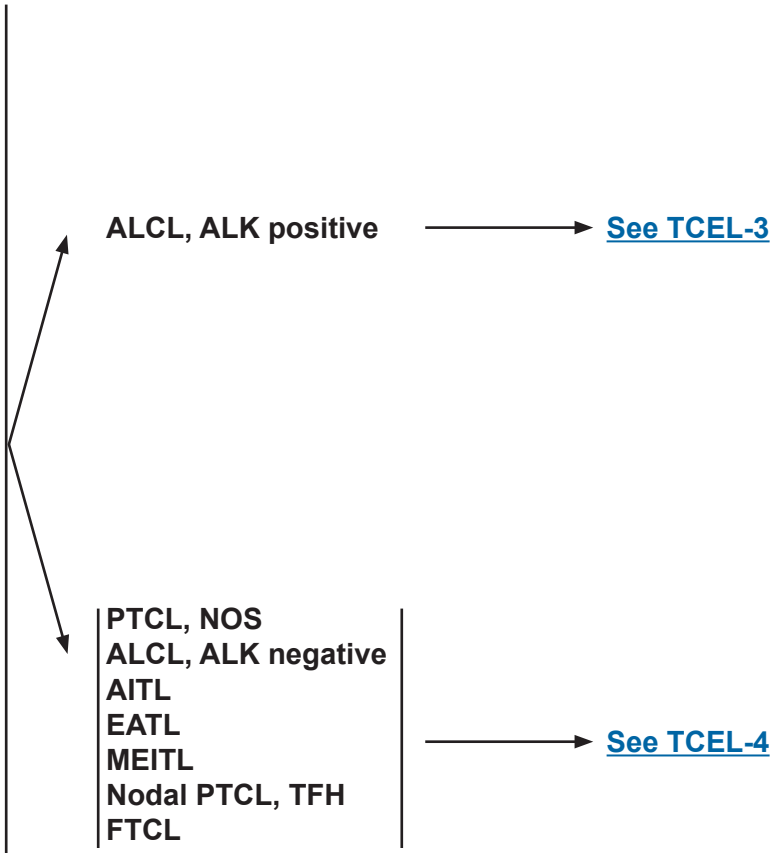
[a] See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (See NCCN Guidelines for B-cell Lymphomas).
[b] TCR clonal gene rearrangements alone are not sufficient for diagnosis, as these are often seen with reactive/inflammatory processes.
[c]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

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.

WORKUP

ESSENTIAL:[h]
- History and 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 with differential
- Bone marrow biopsy ± aspirate
- LDH
- Comprehensive metabolic panel
- Uric acid
- PET/CT scan and/or chest/abdominal/pelvic (C/A/P) CT with contrast of diagnostic quality
- Calculation of International Prognostic Index (IPI)[i]
- 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
- HIV testing
- Hepatitis B testing
- Consider quantitative EBV PCR
- Consider celiac disease in newly diagnosed EATL
- Discussion of fertility issues and sperm banking



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

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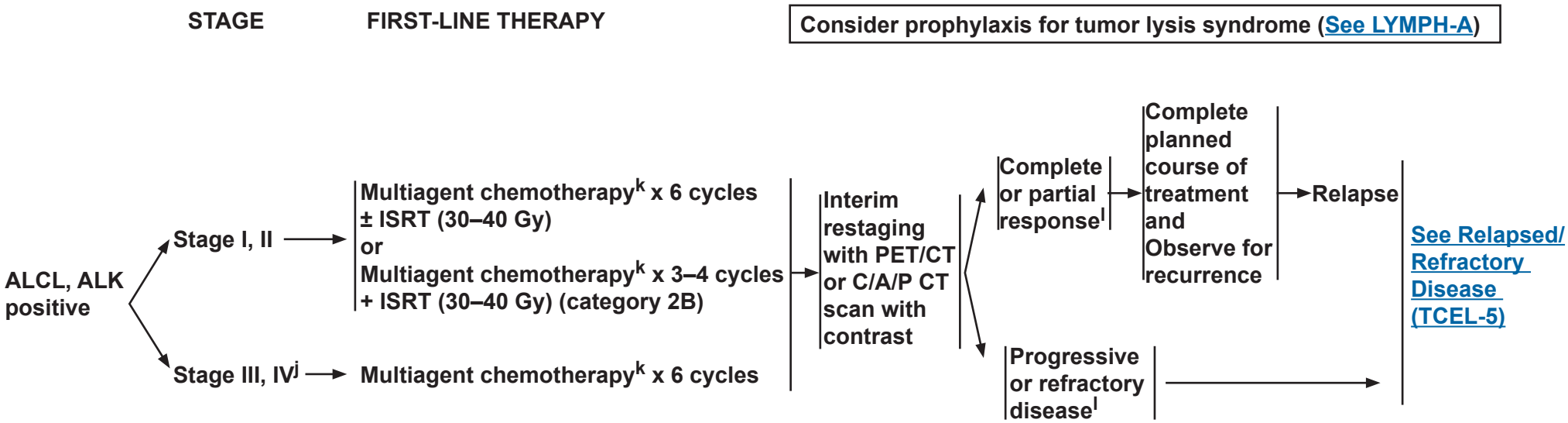
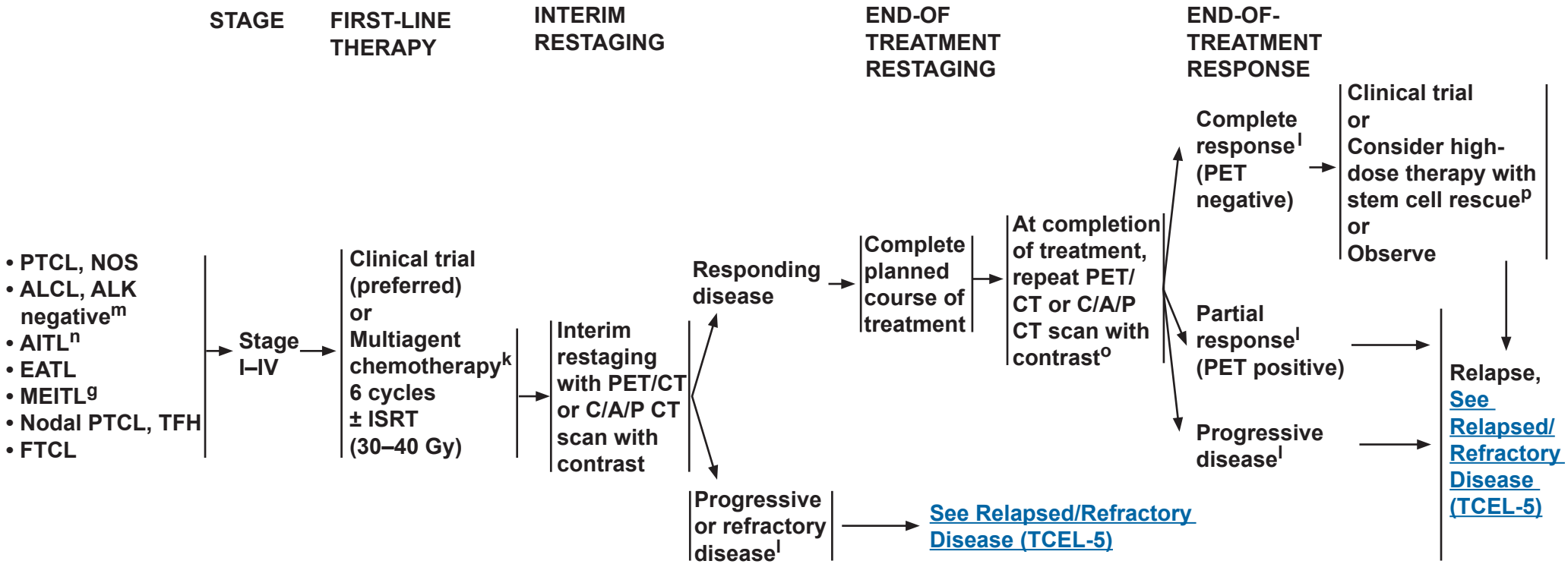


[j]Consider consolidative HDT/ASCR for high-risk IPI patients in CR1.
[k]See Suggested Treatment Regimens (TCEL-B).
[l]See Lugano Response Criteria for Non-Hodgkin's Lymphoma (LYMP-B).

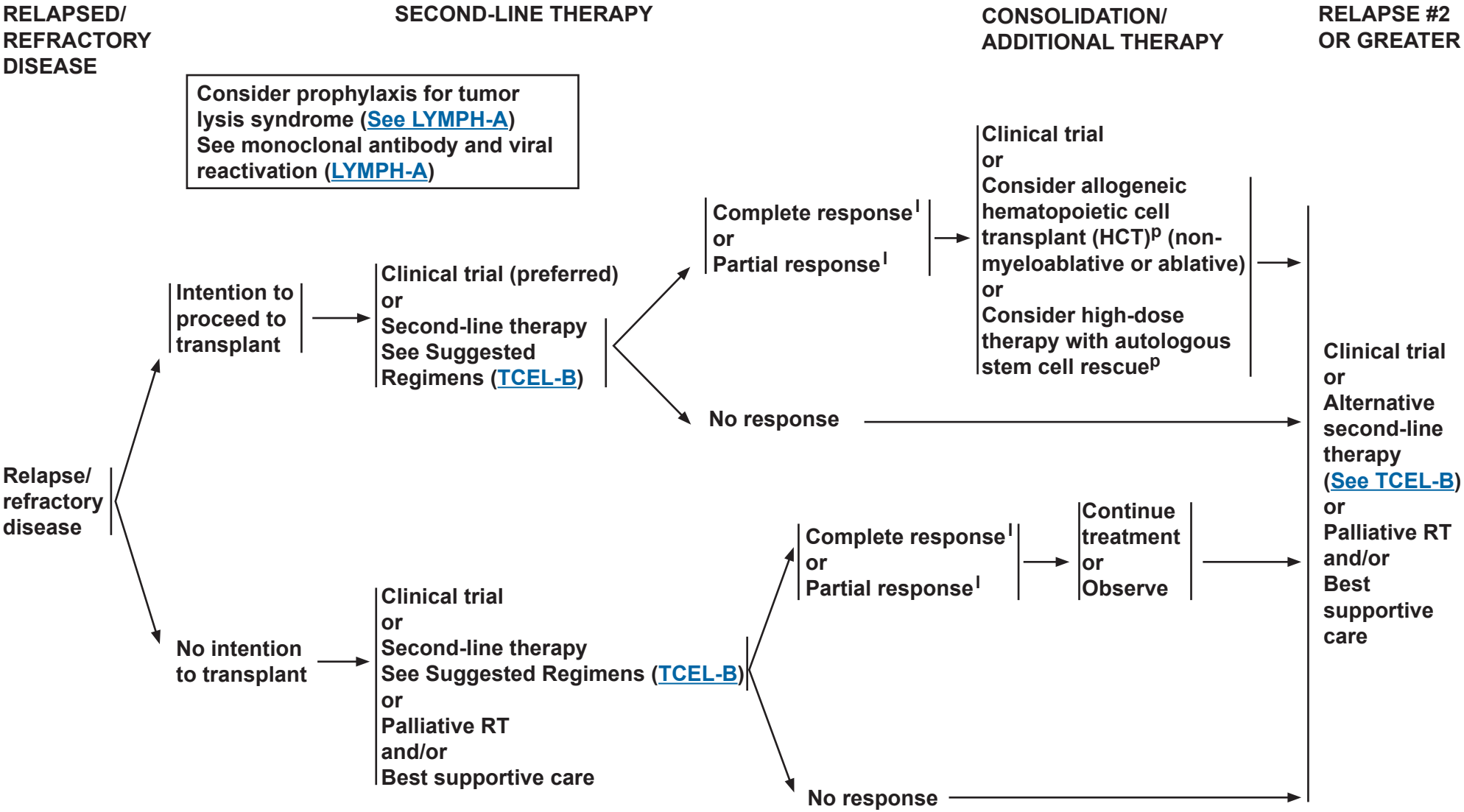
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



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

[g]MEITL has only recently been separated as its own entity and optimal treatment has not been defined.
[k]See Suggested Treatment Regimens (TCEL-B).
[l]See Lugano Response Criteria for Non-Hodgkin's Lymphoma (LYMP-B).
[m]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.)
[n]For selected patients (elderly, comorbid conditions), a trial of single-agent corticosteroid may be considered for symptom management.
[o]If PET/CT scan positive, rebiopsy before changing course of treatment.
[p]Localized areas can be irradiated before or after high-dose therapy.

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.



[I] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (LYMP-B).
[p] Localized areas can be irradiated before or after high-dose therapy.

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.

INTERNATIONAL PROGNOSTIC INDEX[a]

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

AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX[a]

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

PROGNOSTIC INDEX FOR PTCL-U (PIT)[b]

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

PROGNOSTIC INDEX FOR PTCL-U (modified-PIT)[c]

RISK FACTORS:	PROGNOSTIC RISK:	
• Age >60 years	• Group 1	0 or 1
• Serum LDH > normal	• Group 2	2
• ECOG performance status 2–4	• Group 3	3 or 4
• Ki67 ≥80%		

INTERNATIONAL T-CELL LYMPHOMA PROJECT[d]

RISK FACTORS:		
• Age >60 years	• Group 1	0
• ECOG performance status 2–4	• Group 2	1
• Platelet count (<150 x 10^9/L)	• Group 3	2
	• Group 4	3

[a]The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-hodgkin's lymphoma. N Engl J Med 1993;329:987-994.
[b]Gallamini A, Stelitano C, Calvi R, et al. Peripheral T-cell lymphoma unspecified (PTCL-U): A new prognostic model from a retrospective multicentric clinical study. Blood 2004;103:2474-2479.
[c]Went P, Agostinelli C, Gallamini A, et al. Marker expression in peripheral T-cell lymphoma: a proposed clinical-pathologic prognostic score. J Clin Oncol 2006;24:2472-2479.
[d]Vose JM. International peripheral T-cell lymphoma (PTCL) clinical and pathologic review project: poor outcome by prognostic indices and lack of efficacy with anthracyclines [abstract]. Blood 2005;106(11):Abstract 811a.

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[a]

First-line Therapy:

- **Clinical trial[b]**
- **ALCL, ALK+ histology**
  - **CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)**
  - **CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone)**
  - **Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)**
- **Other histologies:[c,d,e]**
  - **Preferred regimens (in alphabetical order)**
    - ◊ **CHOEP**
    - ◊ **CHOP**
    - ◊ **Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)**
  - **Other recommended regimens (in alphabetical order)**
    - ◊ **CHOP followed by IVE (ifosfamide, etoposide, epirubicin) alternating with intermediate-dose methotrexate [Newcastle Regimen] [studied only in patients with EATL][f]**
    - ◊ **HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with high-dose methotrexate and cytarabine (category 3)**

First-line Consolidation:

- **Consider consolidation with high-dose therapy and stem cell rescue.**

See Second-line and Subsequent Therapy:

- **PTCL-NOS; EATL; MEITL; Nodal PTCL, TFH; FTCL (TCEL-B 2 of 5)**
- **AITL (TCEL-B 3 of 5)**
- **ALCL (TCEL-B 4 of 5)**

[a]See references for regimens on TCEL-B 5 of 5.
[b]While anthracycline-based 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]Other histologies include ALCL, ALK-; PTCL, NOS; AITL; EATL; MEITL; Nodal PTCL, TFH; FTCL.
[d]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.)
[e]MEITL has only recently been separated as its own entity and optimal treatment has not been defined.
[f]CHOP followed by IVE regimen includes HCT.

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 FOR PTCL-NOS, EATL; MEITL; Nodal PTCL, TFH; FTCL[a,e]

Second-line Therapy (with intention to proceed to transplant) and Subsequent Therapy

- Clinical trial preferred
- Preferred regimens
  - Single agents (alphabetical order)
    - ◊ Belinostat
    - ◊ Brentuximab vedotin for CD30+ PTCL[g]
    - ◊ 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)
- Other recommended regimens
  - Single agents (alphabetical order)
    - ◊ Bendamustine
    - ◊ Gemcitabine
    - ◊ Lenalidomide
  - Combination regimen
    - ◊ GVD (gemcitabine, vinorelbine, liposomal doxorubicin[h]

Second-line Therapy (no intention to transplant) and Subsequent Therapy:

- Clinical trial preferred
- Preferred single agents (alphabetical order)
  - Belinostat
  - Brentuximab vedotin for CD30+ PTCL[g]
  - Pralatrexate
  - Romidepsin
- Other recommended single agents (alphabetical order)
  - Alemtuzumab[i]
  - Bendamustine
  - Bortezomib[j] (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)

[a]See references for regimens on TCEL-B 5 of 5.
[e]MEITL has only recently been separated as its own entity and optimal treatment has not been defined.
[g]Interpretation of CD30 expression is not standardized. Responses have been seen in patients with a low level of CD30-positivity.
[h]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.
[i]While alemtuzumab is no longer commercially available, it may be obtained for clinical use.
[j]Activity has been demonstrated in small clinical trials and additional larger trials are needed.

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 FOR AITL[a]

Second-line Therapy (with intention to proceed to transplant) and Subsequent Therapy

- Clinical trial preferred
- Preferred regimens
  - Single agents (alphabetical order)
    - ◊ Belinostat
    - ◊ Brentuximab vedotin for CD30+ AITL[g]
    - ◊ 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)
- Other recommended regimens
  - Single agents (alphabetical order)
    - ◊ Bendamustine
    - ◊ Gemcitabine
    - ◊ Lenalidomide
    - ◊ Pralatrexate[k]

Second-line Therapy (no intention to transplant) and Subsequent Therapy:

- Clinical trial preferred
- Preferred single agents (alphabetical order)
  - Belinostat
  - Brentuximab vedotin for CD30+ AITL[g]
  - Romidepsin
- Other recommended single agents (alphabetical order)
  - Alemtuzumab[i]
  - Bendamustine
  - Bortezomib[j] (category 2B)
  - Cyclosporine[l]
  - Gemcitabine
  - Lenalidomide
  - Pralatrexate[k]
  - Radiation therapy

[a]See references for regimens on TCEL-B 5 of 5.
[g]Interpretation of CD30 expression is not standardized. Responses have been seen in patients with a low level of CD30-positivity.
[i]While alemtuzumab is no longer commercially available, it may be obtained for clinical use.
[j]Activity has been demonstrated in small clinical trials and additional larger trials are needed
[k]In AITL, pralatrexate has limited activity.
[l]With close follow-up of renal function.

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

See Second-line and Subsequent Therapy:
- PTCL-NOS; EATL; MEITL; Nodal PTCL, TFH; FTCL (TCEL-B 2 of 5)
- ALCL (TCEL-B 4 of 5)

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 FOR ALCL[a]

Second-line Therapy (with intention to proceed to transplant) and Subsequent Therapy

- Clinical trial preferred
- Preferred regimen
  - Brentuximab vedotin
- Other recommended regimens
  - Single agents (alphabetical order)
    - Belinostat
    - Bendamustine
    - Crizotinib (ALK+ ALCL only)
    - Gemcitabine
    - 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 regimen
  - Brentuximab vedotin
- Other recommended single agents (alphabetical order)
  - Belinostat
  - Bendamustine
  - Bortezomib[j] (category 2B)
  - Crizotinib (ALK+ ALCL only)
  - Gemcitabine
  - Pralatrexate
  - Radiation therapy
  - Romidepsin

See First-line Therapy on TCEL-B 1 of 5.
See Second-line and Subsequent Therapy:
- PTCL-NOS; EATL; MEITL; Nodal PTCL, TFH; FTCL (TCEL-B 2 of 5)
- AITL (TCEL-B 3 of 5)

[a]See references for regimens on TCEL-B 5 of 5.
[j]Activity has been demonstrated in small clinical trials and additional larger trials are needed.

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

First-line Therapy

CHOP

Savage KJ, Chhanabhai M, Gascoyne RD, Connors JM. Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification. Ann Oncol 2004;15:1467-1475.

CHOP or CHOP-14 with or without etoposide

Pfreundschuh M, Trümper L, Kloess M, et al. German High-Grade Non-Hodgkin's Lymphoma Study Group. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: results of the NHL-B1 trial of the DSHNHL. Blood 2004;104:626-33.

Pfreundschuh M, Trümper L, Kloess M, et al. German High-Grade Non-Hodgkin's Lymphoma Study Group. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: Results of the NHL-B2 trial of the DSHNHL. Blood 2004;104:634-41.

Schmitz N, Trumper L, Ziepert M, et al. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood 2010;116:3418-3425.

CHOP followed by IVE

Sieniawski M, Angamuthu N, Boyd K, et al. Evaluation of enteropathy-associated T-cell lymphoma comparing standard therapies with a novel regimen including autologous stem cell transplantation. Blood 2010;115:3664-3670.

Dose-adjusted EPOCH

Dunleavy K, Shovlin M, Pittaluga S, et al. DA-EPOCH Chemotherapy is highly effective in ALK-positive and ALK-negative ALCL: Results of a prospective study of PTCL subtypes in adults [abstract]. Blood 2011;118:Abstract 1618.

Wilson WH, Bryant G, Bates S, et al. EPOCH chemotherapy: toxicity and efficacy in relapsed and refractory non-Hodgkin's lymphoma. J Clin Oncol 1993;11:1573-582.

Peng YL, Huang HQ, Lin XB, et al. [Clinical outcomes of patients with peripheral T-cell lymphoma (PTCL) treated by EPOCH regimen]. Ai Zheng 2004;23:943-946.

Dunleavy K, Pittaluga S, Shovlin M, et al. Phase II trial of dose-adjusted EPOCH in untreated systemic anaplastic large cell lymphoma. Haematologica 2018; 101: e27–e29.

HyperCVAD alternating with high-dose methotrexate and cytarabine

Escalon MP, Liu NS, Yang Y, et al. Prognostic factors and treatment of patients with T-cell non-Hodgkin lymphoma: the M. D. Anderson Cancer Center experience. Cancer 2005;103:2091-2098.

Pozadzides JV, Perini G, Hess M, et al. Prognosis and treatment of patients with peripheral T-cell lymphoma: The M. D. Anderson Cancer Center experience [abstract]. J Clin Oncol 2010;28: Abstract 8051.

Second-line Therapy

Alemtuzumab

Enblad G, Hagberg H, Erlanson M, et al. A pilot study of alemtuzumab (anti-CD52 monoclonal antibody) therapy for patients with relapsed or chemotherapy-refractory peripheral T-cell lymphomas. Blood 2004;103:2920-2924.

Belinostat

O'Connor OA, Horwitz S, Masszi T, et al. Belinostat in patients with relapsed or refractory peripheral T-cell lymphoma: Results of the pivotal phase II BELIEF (CLN-19) study. J Clin Oncol 2015;33:2492-2499.

Bendamustine

Damaj G, Gressin R, Bouabdallah K, et al. Results from a prospective, open-label, phase II trial of bendamustine in refractory or relapsed T-cell lymphomas: the BENTLY trial. J Clin Oncol 2013;31:104-110.

Bortezomib

Zinzani P, Musuraca G, Tani M, et al. Phase II trial of proteasome inhibitor bortezomib in patients with relapsed or refractory cutaneous T-cell lymphoma. J Clin Oncol 2007;25:4293-4297.

Brentuximab vedotin

Pro B, Advani R, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: Results of a phase II study. J Clin Oncol 2012;30:2190-2196.

Advani RH, Brice P, Bartlett NL, et al. Three-year survival results from an ongoing phase 2 study of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma. Blood 2013;122:1809.

Horwitz SM, Advani RH, Bartlett NL, et al. Objective responses in relapsed T-cell lymphomas with single agent brentuximab vedotin. Blood 2014;123 3095-3100.

Cyclosporine for AITL

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

DHAP (dexamethasone, cisplatin, cytarabine)

Velasquez WS, Cabanillas F, Salvador P, et al. Effective salvage therapy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone (DHAP). Blood 1988;71:117-122.

Mey UJ, Orlopp KS, Flieger D, et al. Dexamethasone, high-dose cytarabine, and cisplatin in combination with rituximab as salvage treatment for patients with relapsed or refractory aggressive non-Hodgkin's lymphoma. Cancer Invest 2006;24:593-600.

ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)

Velasquez WS, McLaughlin P, Tucker S, et al. ESHAP - an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. J Clin Oncol 1994;12:1169-1176.

Gemcitabine

Zinzani PL, Baliva G, Magagnoli M, et al. Gemcitabine treatment in pretreated cutaneous T-cell lymphoma: Experience in 44 patients. J Clin Oncol 2000;18:2603-2606.

Zinzani PL, Magagnoli M, Bendandi M, et al. Therapy with gemcitabine in pretreated peripheral T-cell lymphoma patients. Ann Oncol 1998;9:1351-1353.

GDP (gemcitabine, dexamethasone, cisplatin)

Crump M, Baetz T, Couban S, et al. Gemcitabine, dexamethasone, and cisplatin in patients with recurrent or refractory aggressive histology B-cell non-Hodgkin lymphoma: a Phase II study by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG). Cancer 2004;101:1835-1842.

Dong M, He XH, Liu P, et al. Gemcitabine-based combination regimen in patients with peripheral T-cell lymphoma. Med Oncol 2013;30:351.

Connors JM, Sehn LH, Villa D, et al. Gemcitabine, dexamethasone, and cisplatin (GDP) as secondary chemotherapy in relapsed/refractory peripheral T-cell lymphoma [abstract]. Blood 2013;122:Abstract 4345.

GND (gemcitabine, vinorelbine, liposomal doxorubicin)

Qian Z, Song Z, Zhang H, et al. Gemcitabine, navelbine, and doxorubicin as treatment for patients with refractory or relapsed T-cell lymphoma. Biomed Res Int. 2015;2015:606752.

GemOX (gemcitabine, oxaliplatin)

Lopez A, Gutierrez A, Palacios A, et al. GEMOX-R regimen is a highly effective salvage regimen in patients with refractory/relapsing diffuse large-cell lymphoma: A phase II study. Eur J Haematol 2008;80:127-132.

ICE (ifosfamide, carboplatin, etoposide)

Zelenetz AD, Hamlin P, Kewalramani T, et al. Ifosfamide, carboplatin, etoposide (ICE)-based second-line chemotherapy for the management of relapsed and refractory aggressive non-Hodgkin's lymphoma. Ann Oncol 2003;14[suppl 1]:i5-10.

Lenalidomide

Morschhauser, Fitoussi O, Haioun C, et al. A phase 2, multicentre, single-arm, open-label study to evaluate the safety and efficacy of single-agent lenalidomide (Revlimid) in subjects with relapsed or refractory peripheral T-cell non-Hodgkin lymphoma: the EXPECT trial. Eur J Cancer 2013;49:2869-2876.

Toumishey E, Prasad A, Dueck G, et al. Final report of a phase 2 clinical trial of lenalidomide monotherapy for patients with T-cell lymphoma. Cancer 2015;121:716-723.

Pralatrexate

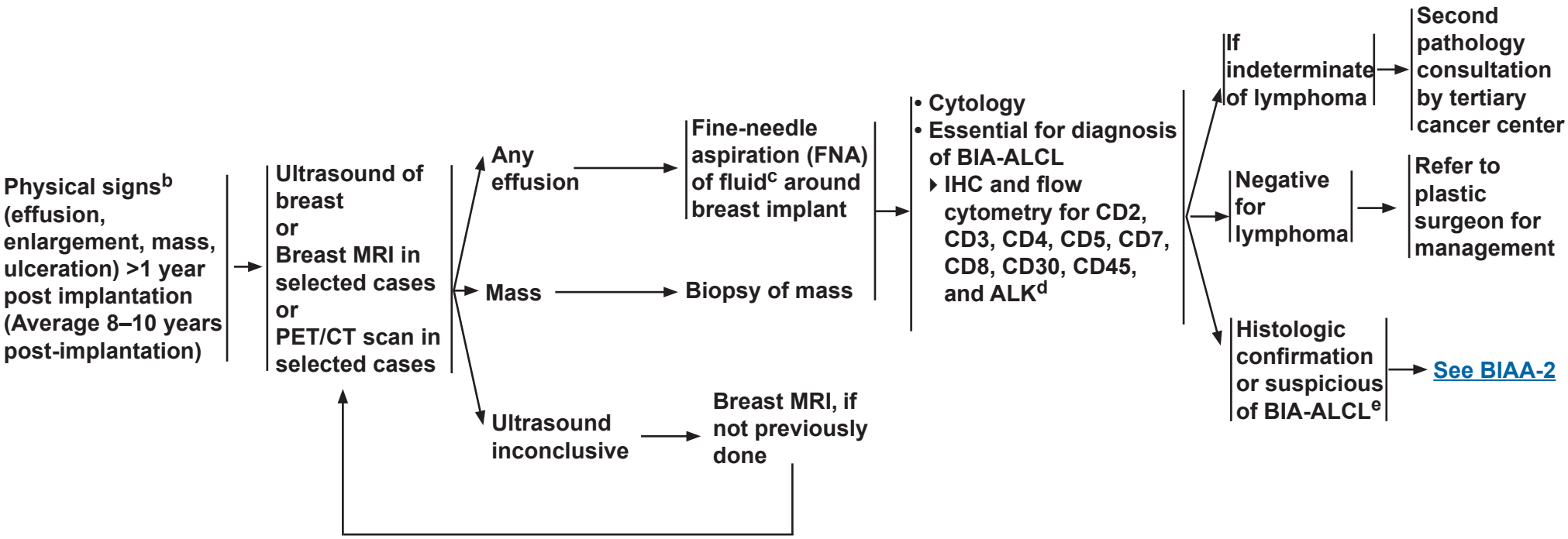
O'Connor OA, Pro B, Pinter-Brown L, et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: Results from the pivotal PROPEL study. J Clin Oncol 2011;29:1182-1189.

Romidepsin

Coiffier B, Pro B, Prince HM, et al. Results From a Pivotal, Open-Label, Phase II Study of Romidepsin in Relapsed or Refractory Peripheral T-Cell Lymphoma After Prior Systemic Therapy. J Clin Oncol 2012;30:631-636.

Coiffier B, Pro B, Prince HM, et al. Romidepsin for the treatment of relapsed/refractory peripheral T-cell lymphoma: pivotal study update demonstrates durable responses. J Hematol Oncol 2014;7:11.

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.



See References on BIAA-A

[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.
[b]A majority of cases have been seen in textured implants (Miranda RN, et al. J Clin Oncol 2014;32:114-120).
[c]Larger volume of fluid yields a more accurate diagnosis.
[d]Breast implant-associated ALCL (BIA-ALCL) is usually ALK-negative but has a good prognosis.
[e]FDA recommends reporting all BIA-ALCL cases to the PROFILE Registry: www.thepsf.org/PROFILE.

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 3.2018
Breast Implant-Associated ALCL

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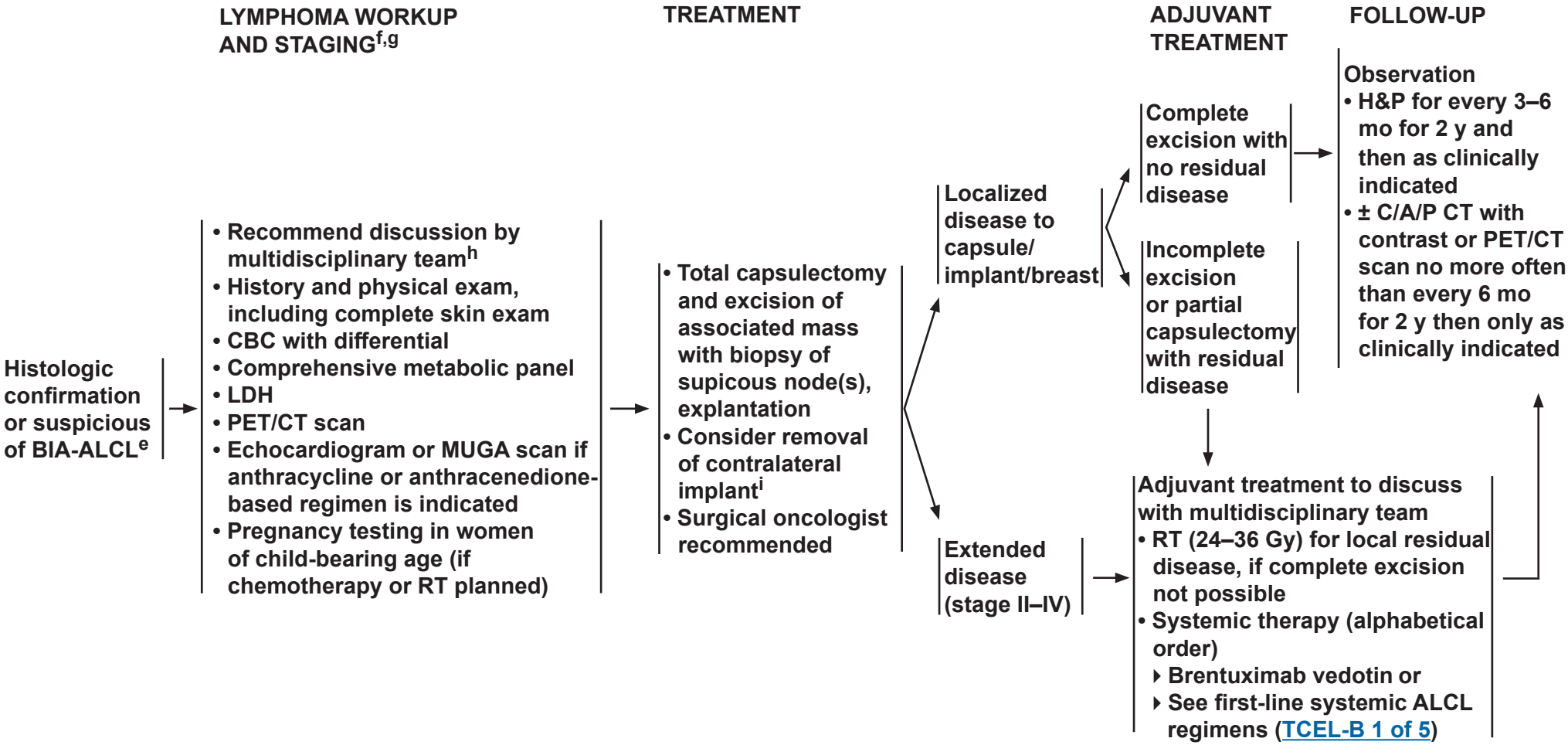
Discussion



[e]FDA recommends reporting all BIA-ALCL cases to the PROFILE Registry: www.thepsf.org/PROFILE.

See References on BIAA-A

[f]See Proposed TNM Staging for Breast Implant–Associated Anaplastic Large-Cell Lymphoma (BIAA-B).

[g]For BIA-ALCL, bone marrow biopsy is *only* needed in selected cases (eg, extensive disease or unexplained cytopenia).

[h]Eg, oncologist, surgical oncologist, plastic surgeon, hemepathologist.

[i]In approximately 4.6% of cases, lymphoma was found in the contralateral breast (Clemens MW, Medeiros LJ, Butler CE, et al. J Clin Oncol 2018; 34:160-168)

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

Adrada BE, et al. Breast implant-associated anaplastic large cell lymphoma: sensitivity, specificity, and findings of imaging studies in 44 patients. Breast Cancer Res Treat 2014;147:1-14.

Miranda RN, et al. Breast implant-associated anaplastic large-cell lymphoma: long-term follow-up of 60 patients. J Clin Oncol 2014;32:114-120.

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 2018;34:160-168.

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Pro B, Advani R, Brice P, et al. Four-year survival data from an ongoing pivotal phase 2 study of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma [abstract]. Blood 2014 124:Abstract 3095.

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.

Proposed TNM Staging for Breast Implant–Associated Anaplastic Large-Cell Lymphoma*

TNM	Description
T: tumor extent	
T1	Confined to effusion or a layer on luminal side of capsule
T2	Early capsule infiltration
T3	Cell aggregates or sheets infiltrating the capsule
T4	Lymphoma infiltrates beyond the capsule
N: lymph node	
N0	No lymph node involvement
N1	One regional lymph node (+)
N2	Multiple regional lymph nodes (+)
M: metastasis	
M0	No distant spread
M1	Spread to other organs/distant sites

Stage Designation	Description
IA	T1 N0 M0
IB	T2 N0 M0
IC	T3 N0 M0
IIA	T4 N0 M0
IIB	T1-3 N1 M0
III	T4 N1-2 M0
IV	Tany Nany M1

*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 2018;34:160-168.

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.

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[a]**
- **IHC panel of skin biopsy[b,c,d]**
  - **CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, CD25, CD56, TIA1, granzyme B, ßF1, TCR-CγM1**
- **Molecular analysis to detect clonal T-cell antigen receptor (TCR) gene rearrangements[e] or other assessment of clonality[f]**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **Assessment of peripheral blood for Sezary cells (in extensive skin disease where skin biopsy is not diagnostic, and/or strongly of advanced-stage disease) 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)**
- **Core needle biopsy (FNA is often inadequate) of suspicious lymph nodes (if biopsy of skin is not diagnostic)**
- **Assessment of HTLV-1[g] by serology or other methods in at-risk populations.**

→ See Workup (MFSS-2)

[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.

[b]Clinically suspicious and ~~or~~ histologically non-diagnostic cases. Pimpinelli N, Olsen EA, Santucci M, et al, for the International Society for Cutaneous Lymphoma. Defining early mycosis fungoides. J Am Acad Dermatol 2005;53:1053-1063.

[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 immunophenotype: CD2+ CD3+ CD5+ CD7- CD4+ CD8- (rarely CD8+) CD30-/+ cytotoxic granule proteins negative.

[e]TCR clonal gene rearrangement results should be interpreted with caution. TCR clonal gene 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. A negative PCR in the setting of high clinical suspicion does not exclude the diagnosis of MF.

[f]Such as FISH, karyotype, genomic analysis.

[g]See map for prevalence of HTLV-1 by geographic region.

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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:

- History and complete physical examination:
  - Complete skin examination: 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:[h]
  - CBC with Sezary screen (manual slide review, "Sezary cell prep")
  - Sezary flow cytometric study (optional for T1[i])
  - TCR gene rearrangement in peripheral blood lymphocytes if blood involvement suspected
  - Comprehensive metabolic panel
  - LDH
- Imaging studies:
  - C/A/P CT with contrast or integrated whole body PET/CT (arms/legs included when disease assessment of entire body is needed); for ≥T2b or large cell transformed or folliculotropic MF, or with palpable adenopathy or abnormal laboratory studies; consider for T2a (patch disease with ≥10% BSA)

USEFUL IN SELECTED CASES:

- Bone marrow biopsy in patients with unexplained hematologic abnormality
- Core needle 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
- Pregnancy testing in women of child-bearing age if contemplating treatments that are contraindicated in pregnancy[j]

STAGE
(MFSS-3 and MFSS-4)

- Stage IA → See Primary Treatment (MFSS-5)
- Stage IB-IIA → See Primary Treatment (MFSS-6)
- Stage IIB → See Primary Treatment (MFSS-7)
- Stage III → See Primary Treatment (MFSS-8)
- Stage IV → See Primary Treatment (MFSS-9)

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

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TNMB		TNMB Classification and Staging of Mycosis Fungoides and Sezary Syndrome[k,l]
Skin	T1	Limited patches,[m] papules, and/or plaques[n] covering <10% of the skin surface
	T2	Patches,[m] papules, and/or plaques[m] covering ≥10% of the skin surface
	T2a	Patch only
	T2b	Plaque ± patch
	T3	One or more tumors[o] (≥1 cm in diameter)
	T4	Confluence of erythema ≥80% body surface area
Node	N0	No abnormal lymph nodes; biopsy not required
	N1	Abnormal lymph nodes; histopathology Dutch Gr 1 or NCI LN 0-2
	N2	Abnormal lymph nodes; histopathology Dutch Gr 2 or NCI LN 3
	N3	Abnormal lymph nodes; histopathology Dutch Gr 3-4 or NCI LN 4
	NX	Abnormal lymph nodes; no histologic confirmation
Visceral	M0	No visceral organ involvement
	M1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
	MX	Abnormal visceral site; no histologic confirmation
Blood	B0	Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes or <250/mcL are atypical (Sezary) cells or <15% CD4+/CD26- or CD4+/CD7- cells of total lymphocytes
	B1	Low blood tumor burden: >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
	B2	High blood tumor burden: ≥1000/mcL Sezary cells[l] (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

See NCI Lymph Node Classification on MFSS-4

[k]Adapted from Olsen E, Vonderheid E, Pimpinelli N, et al. Blood 2007;110:1713-1722 and Olsen E, Whittaker S, Kim Y, et al. J Clin Oncol 2011;29:2598-2607.
[l]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).
[m]Patch = Any size skin lesion without significant elevation or induration.
Presence/absence of hypo- or hyperpigmentation, scale, crusting, and/or poikiloderma should be noted.
[n]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.
[o]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 Staging of MF and SS[k]

	T	N	M	B
IA	1	0	0	0,1
IB	2	0	0	0,1
IIA	1–2	1,2	0	0,1
IIB	3	0–2	0	0,1
IIIA	4	0–2	0	0
IIIB	4	0–2	0	1
IVA_1	1–4	0–2	0	2
IVA_2	1–4	3	0	0–2
IVB	1–4	0–3	1	0–2

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

Clendenning WE, Rappaport HW. Report of the Committee on Pathology of Cutaneous T Cell Lymphomas. Cancer Treat Rep 1979;63:719-724.

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

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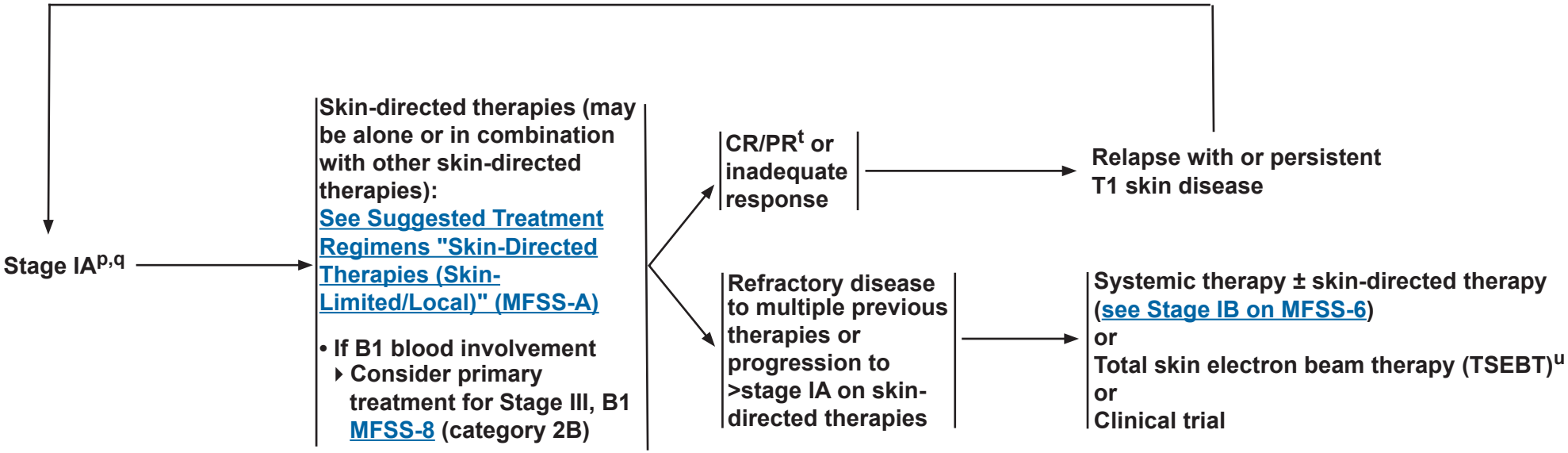
STAGE (MFSS-3 and MFSS-4)

PRIMARY TREATMENT[r]

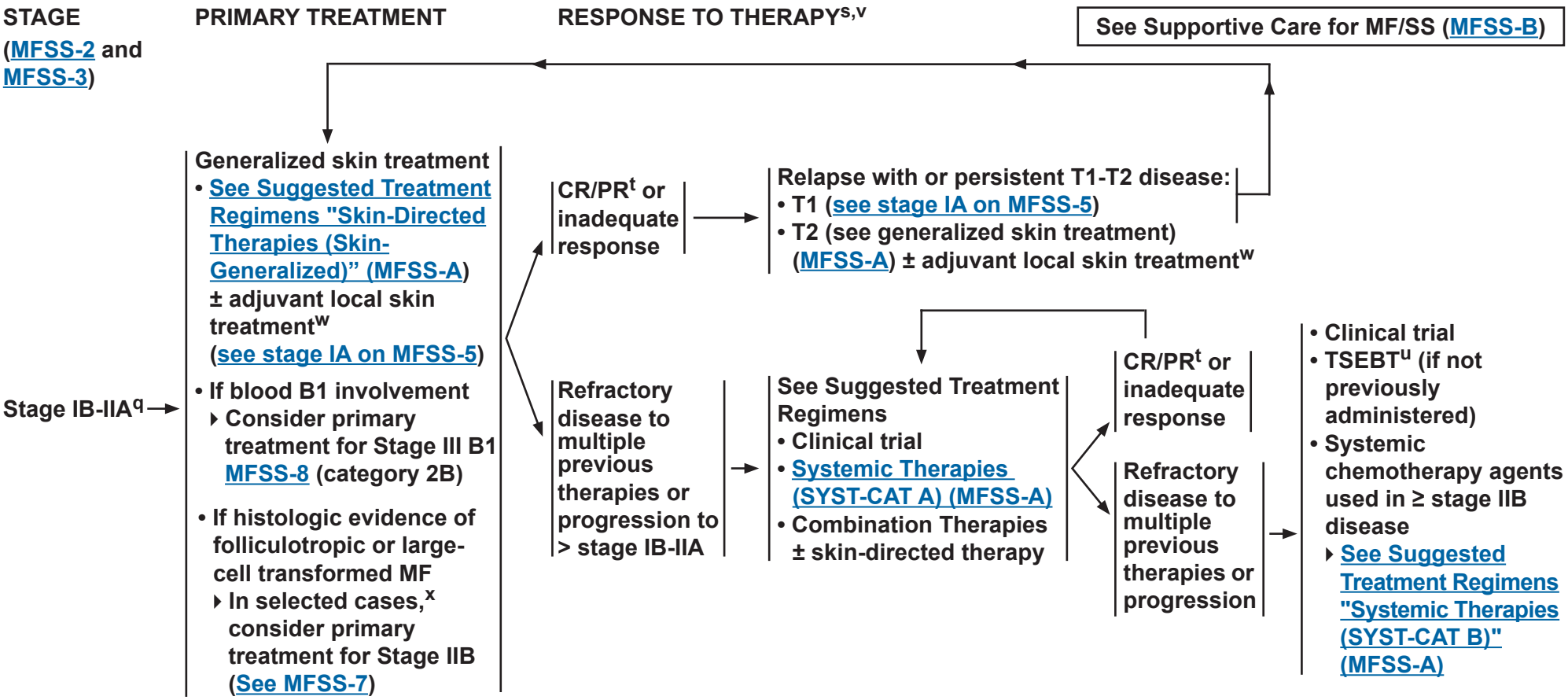
RESPONSE TO THERAPY[s]

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



[p]In rare cases of confirmed unilesional MF, RT has been shown to provide long-term remission.
[q]It is preferred that treatment occur at centers with expertise in the management of the disease.
[r]In patients with folliculotropism or histologic large-cell transformed MF, skin disease may be less responsive to topical therapies.
[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).
[t]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 responds 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.
[u]See Principles of Radiation Therapy For MF/SS. (MFSS-C).

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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[u]See Principles of Radiation Therapy For MF/SS (MFSS-C).
[v]Imaging indicated when suspicious of clinical extracutaneous disease with modalities used in workup.
[w]For patients with recalcitrant sites after generalized skin treatment, additional local treatment may be needed.
[x]Histologic evidence of folliculotropic or large-cell transformed MF is associated with higher risk of disease progression.

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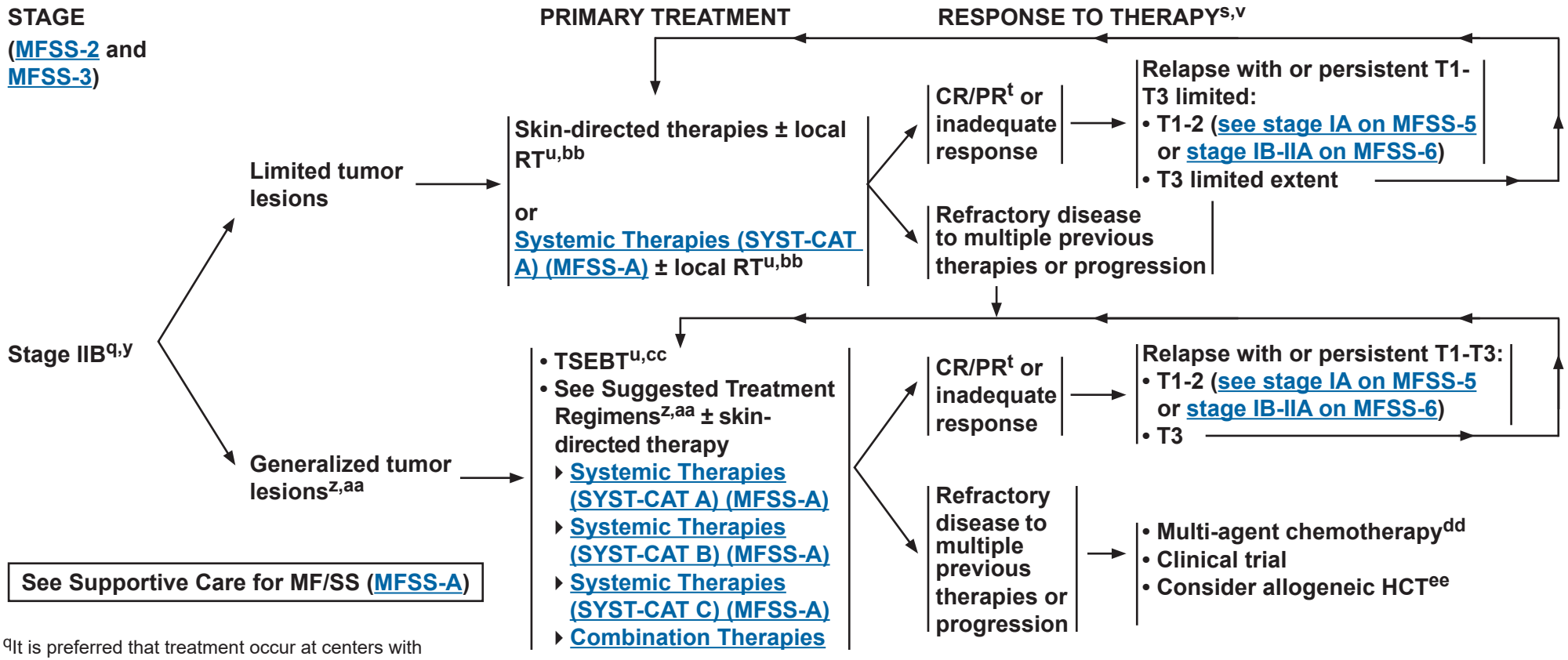

See Supportive Care for MF/SS (MFSS-A)

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[t] 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 responds 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.

[u] See Principles of Radiation Therapy For MF/SS (MFSS-C).

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

[y] Rebiopsy if suspect large-cell transformation.

[z] 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.

[aa] 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.

[bb] RT is preferred for tumor lesions.

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

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

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

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Mycosis Fungoides/Sezary Syndrome

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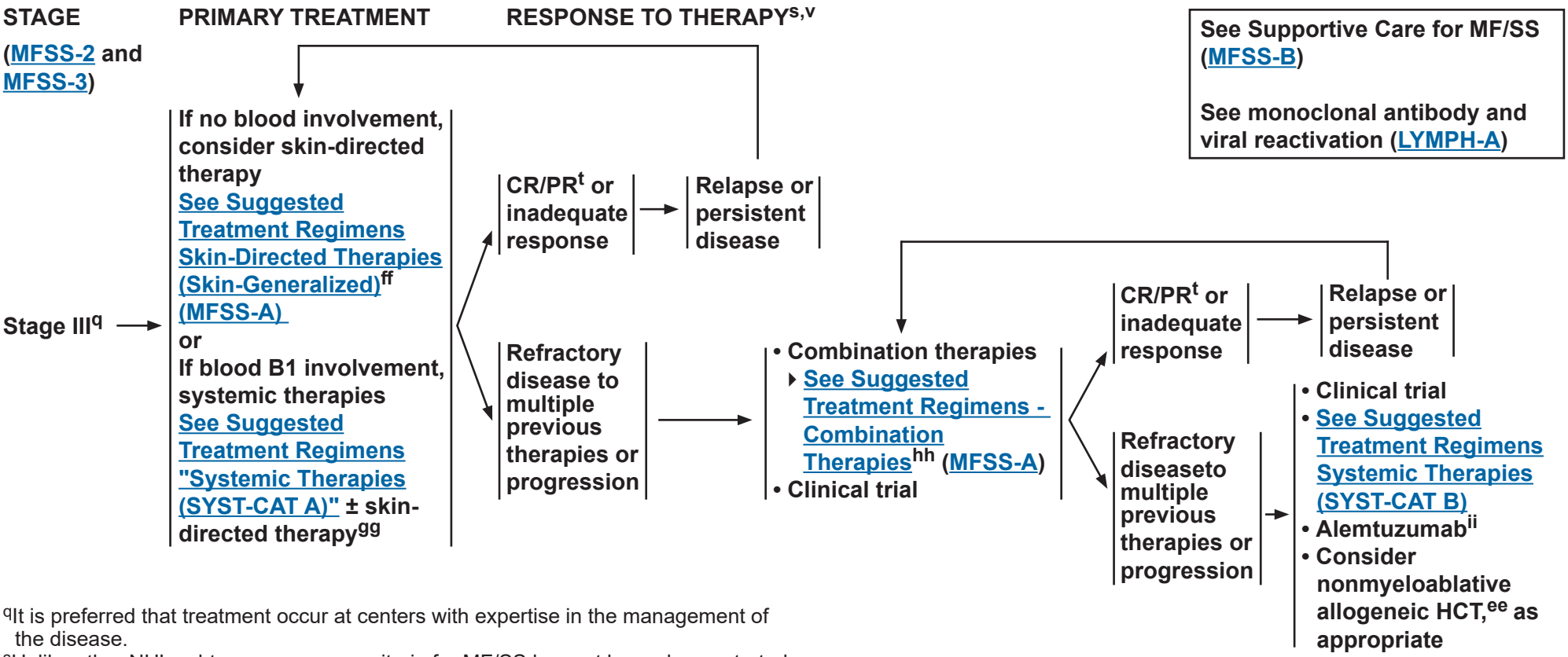

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[s]Unlike other NHL subtypes, response criteria for MF/SS has not been demonstrated to correlate with prognosis. Often decisions to continue or switch therapy are on a clinical basis. However, a proposal for detailed response criteria has been published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

[t]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 responds 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.

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

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

[ff]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.

[gg]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.

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

[ii]Lower doses of alemtuzumab administered subcutaneously have shown lower incidence of infectious complications.

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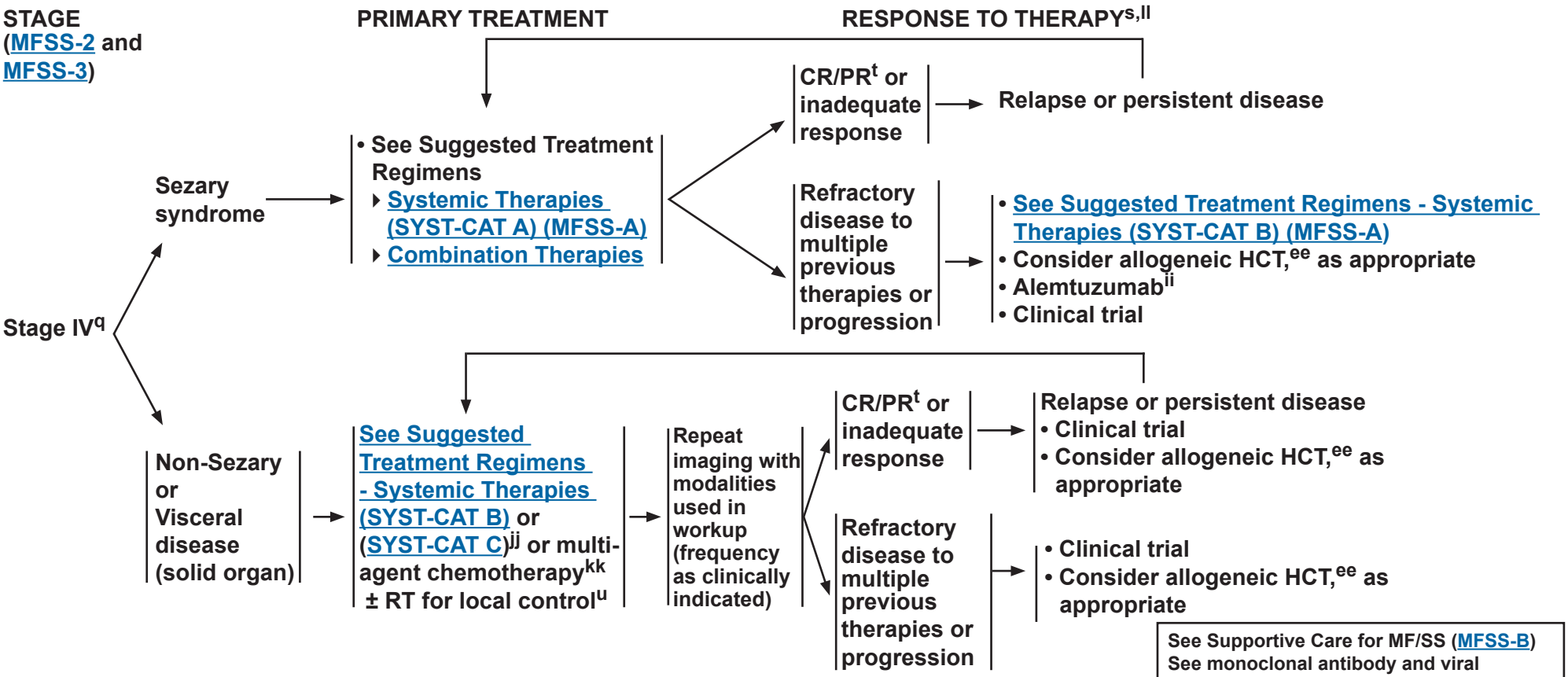

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[u]See Principles of Radiation Therapy For MF/SS (MFSS-C).
[ee]The role of allogeneic HSCT is controversial. See Discussion for further details.
[ii]Lower doses of alemtuzumab administered subcutaneously have shown lower incidence of infectious complications.
[jj]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.
[kk]Consider adjuvant systemic biologic therapy (SYST-CAT A) after chemotherapy to improve response duration.
[ll]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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SUGGESTED TREATMENT REGIMENS[a]

SKIN-DIRECTED THERAPIES

For limited/localized skin involvement (Skin-Limited/Local)
- Topical corticosteroids[b]
- Topical chemotherapy (mechlorethamine [nitrogen mustard])
- Local radiation (8-12 Gy; 24-30 Gy for unilesional presentation)[c]
- Topical retinoids (bexarotene, tazarotene)
- Phototherapy (UVB, NB-UVB for patch/thin plaques; PUVA for thicker plaques)[d]
- Topical imiquimod

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

SYSTEMIC THERAPIES

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

Category B (SYST-CAT B)
- Preferred therapies (alphabetical order)
  - Brentuximab vedotin[h]
  - Gemcitabine
  - Liposomal doxorubicin
  - Low-dose pralatrexate
- Other therapies
  - Chlorambucil
  - Pentostatin
  - Etoposide
  - Cyclophosphamide
  - Temozolomide
  - Methotrexate (>100 mg q week)
  - Pembrolizumab[i] (category 2B)
  - Bortezomib (category 3)

SYSTEMIC THERAPIES (continued)

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

COMBINATION THERAPIES

Skin-directed + Systemic
- Phototherapy + retinoid
- Phototherapy + IFN
- Phototherapy + photopheresis[g]
- Total skin electron beam* + photopheresis[g]

Systemic + Systemic
- Retinoid + IFN
- Photopheresis[g] + retinoid
- Photopheresis[g]+ IFN
- Photopheresis[g] + retinoid + IFN

[a] See references for regimens MFSS-A 2 of 4, MFSS-A 3 of 4, and MFSS-A 4 of 4.

[b] Long-term use of topical steroid may be associated with skin atrophy and/or striae formation. This risk worsens with increased potency of the steroid. High-potency steroid used on large skin surfaces may lead to systemic absorption.

[c] See Principles of Radiation Therapy For MF/SS (MFSS-C).

[d] Cumulative dose of UV is associated with increased risk of UV-associated skin neoplasms; thus, phototherapy may not be appropriate in patients with a history of extensive squamoproliferative skin neoplasms or basal cell carcinomas or who have had melanoma.

[e] It is common practice to follow TSEBT with systemic therapies such as interferon or bexarotene to maintain response.

[f] Safety of combining TSEBT with systemic retinoids or HDAC inhibitors, such as vorinostat or romidepsin, or combining phototherapy with vorinostat or romidepsin is unknown.

[g] Photopheresis may be more appropriate as systemic therapy in patients with some blood involvement (B1 or B2).

[h] A randomized phase 3 trial comparing brentuximab vedotin (BV) with physician's choice of oral bexarotene or methotrexate, showed superior clinical outcome of BV in patients with CD30+ MF and pcALCL. CD30 positivity was defined as CD30 expression ≥10% of total lymphoid cells in at least 1 of minimal 2 skin biopsies required to evaluate for eligibility. Fourty-four percent of eligible patients with MF had at least 1 screening skin biopsy with CD30 <10%. In the two previously reported investigator-initiated studies, clinical responses with BV was observed across all CD30 expression levels including in those with negligible CD30 expression.

[i] Preliminary phase II data in patients with MF and Sezary syndrome. Disease flare is seen in some patients (especially in erythrodermic skin/Sezary patients) and should be distinguished from disease progression. Khodadoust M, Rook A, Porcu P, et al. Pembrolizumab for treatment of relapsed/refractory mycosis fungoides and Sezary syndrome: Clinical efficacy in a CITN multicenter phase 2 study [abstract]. Blood 2018;125:Abstract 181.

[j] Patients with large cell transformed (LCT) MF and stage IV non-Sezary/visceral disease may present with more aggressive growth characteristics. In general, agents listed in SYST-CAT C are preferred in these circumstances.

[k] Combination regimens are generally reserved for patients with relapsed/refractory or extracutaneous 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.

SUGGESTED TREATMENT REGIMENS
References

Skin-directed Therapies

Topical corticosteroids

Zackheim HS, Kashani-Sabet M, Amin S. Topical corticosteroids for mycosis fungoides. Experience in 79 patients. Arch Dermatol 1998;134(8):949-954.

Zackheim HS. Treatment of patch stage mycosis fungoides with topical corticosteroids. Dermatol Ther 2003;16:283-287.

Nitrogen mustard (mechlorethamine hydrochloride)

Kim YH, Martinez G, Varghese A, Hoppe RT. Topical nitrogen mustard in the management of mycosis fungoides: Update of the Stanford experience. Arch Dermatol 2003;139:165-173.

Lessin SR, Duvic M, Guitart J, et al. Topical chemotherapy in cutaneous T-cell lymphoma: positive results of a randomized, controlled, multicenter trial testing the efficacy and safety of a novel mechlorethamine, 0.02%, gel in mycosis fungoides. JAMA Dermatol 2013;149:25-32.

Local radiation

Wilson LD, Kacinski BM, Jones GW. Local superficial radiotherapy in the management of minimal stage IA cutaneous T-cell lymphoma (Mycosis Fungoides). Int J Radiat Oncol Biol Phys 1998;40:109-115.

Neelis KJ, Schimmel EC, Vermeer MH, et al. Low-dose palliative radiotherapy for cutaneous B- and T-cell lymphomas. Int J Radiat Oncol Biol Phys 2009;74:154-158.

Thomas TO, Agrawal P, Guitart J, et al. Outcome of patients treated with a single-fraction dose of palliative radiation for cutaneous T-cell lymphoma. Int J Radiat Oncol Biol Phys 2013;85:747-753

Topical bexarotene

Breneman D, Duvic M, Kuzel T, et al. Phase 1 and 2 trial of bexarotene gel for skin directed treatment of patients with cutaneous T cell lymphoma. Arch Dermatol 2002;138:325-332.

Heald P, Mehlmauer M, Martin AG, et al. Topical bexarotene therapy for patients with refractory or persistent early stage cutaneous T cell lymphoma: results of the phase III clinical trial. J Am Acad Dermatol 2003;49:801-815.

Tazarotene Gel

Apisarnthanarax N, Talpur R, Ward S, Ni X, Kim HW, Duvic M. Tazarotene 0.1% gel for refractory mycosis fungoides lesions: an open-label pilot study. J Am Acad Dermatol 2004;50:600-607.

Topical imiquimod

Deeths MJ, Chapman JT, Dellavalle RP, Zeng C, Aeling JL. Treatment of patch and plaque stage mycosis fungoides with imiquimod 5% cream. J Am Acad Dermatol 2005;52:275-280.

Phototherapy (UVB and PUVA)

Gathers RC, Scherschun L, Malick F, Fivenson DP, Lim HW. Narrowband UVB phototherapy for early stage mycosis fungoides. J Am Acad Dermatol 2002;47:191-197.

Querfeld C, Rosen ST, Kuzel TM, et al. Long term follow up of patients with early stage cutaneous T cell lymphoma who achieved complete remission with psoralen plus UVA monotherapy. Arch Dermatol 2005;141:305-311.

Ponte P, Serrao V, Apetato M. Efficacy of narrowband UVB vs. PUVA in patients with early-stage mycosis fungoides. J Eur Acad Dermatol Venereol 2010;24:716-721.

Olsen EA, Hodak E, Anderson T, et al. Guidelines for phototherapy of mycosis fungoides and Sézary syndrome: A consensus statement of the United States Cutaneous Lymphoma Consortium. J Am Acad Dermatol 2018;74:27-58.

Total skin electron beam therapy (TSEBT)

Chinn DM, Chow S, Kim YH, Hoppe RT. Total skin electron beam therapy with or without adjuvant topical nitrogen mustard or nitrogen mustard alone as initial treatment of T2 and T3 mycosis fungoides. Int J Radiat Oncol Biol Phys 1999;43:951-958.

Ysebaert L, Truc G, Dalac S et al. Ultimate results of radiation therapy for T1-T2 mycosis fungoides. Int J Radiat Oncol Biol Phys 2004;58:1128-1134.

Hoppe RT, Harrison C, Tavallaee M, et al. Low-dose total skin electron beam therapy as an effective modality to reduce disease burden in patients with mycosis fungoides: results of a pooled analysis from 3 phase-II clinical trials. J Am Acad Dermatol 2015;72:286-292.

Morris S, Scarisbrick J, Frew J, et al. The Results of Low-Dose Total Skin Electron Beam Radiation Therapy (TSEB) in Patients With Mycosis Fungoides From the UK Cutaneous Lymphoma Group. Int J Radiat Oncol Biol Phys. 2018;99(3):627-33.

Systemic Therapies

Alemtuzumab for Sezary syndrome ± lymph node disease

Lundin J, Hagberg H, Repp R, et al. Phase 2 study of alemtuzumab (anti-CD52 monoclonal antibody) in patients with advanced mycosis fungoides/Sezary syndrome. Blood 2003;101:4267-4272.

Bernengo MG, Quaglino P, Comessatti A, et al. Low-dose intermittent alemtuzumab in the treatment of Sezary syndrome: clinical and immunologic findings in 14 patients. Haematologica 2007;92:784-794.

Gautschi O, Blumenthal N, Streit M, et al. Successful treatment of chemotherapy-refractory Sezary syndrome with alemtuzumab (Campath-1H). Eur J Haematol 2004;72:61-63.

Querfeld C, Mehta N, Rosen ST, et al. Alemtuzumab for relapsed and refractory erythrodermic cutaneous T-cell lymphoma: a single institution experience from the Robert H. Lurie Comprehensive Cancer Center. Leuk Lymphoma 2009;50:1969-1976.

Bortezomib

Zinzani PL, Musuraca G, Tani M, et al. Phase II trial of proteasome inhibitor bortezomib in patients with relapsed or refractory cutaneous T-cell lymphoma. J Clin Oncol 2007;25:4293-4297.

Brentuximab vedotin

Duvic M, Tetzlaff M, Gangar P, et al. Results of a Phase II Trial of Brentuximab Vedotin for CD30+ Cutaneous T-Cell Lymphoma and Lymphomatoid Papulosis. J Clin Oncol 2015;33:3759-3765

Kim YH, Tavallaee M, Sundram U, et al. Phase II investigator-initiated study of brentuximab vedotin in mycosis fungoides and Sezary syndrome with variable CD30 expression level: A multi-institution collaborative project. J Clin Oncol 2015;33:3750-3758.

Prince HM, Kim YH, Horwitz SM, et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. The Lancet 2018;390:555-566.

Retinoids

Zhang C, Duvic M. Treatment of cutaneous T-cell lymphoma with retinoids. Dermatol Ther 2006;19:264-271.

Duvic M, Martin AG, Kim Y, et al. Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. Arch Dermatol 2001;137:581-593.

Duvic M, Hymes K, Heald P, et al. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. J Clin Oncol 2001;19:2456-2471.

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Continued on next page

SUGGESTED TREATMENT REGIMENS
References

Systemic Therapies Continued

Interferon

Olsen EA. Interferon in the treatment of cutaneous T-cell lymphoma. Dermatol Ther 2003;16:311-321.

Kaplan EH, Rosen ST, Norris DB, et al. Phase II study of recombinant human interferon gamma for treatment of cutaneous T-cell lymphoma. J Natl Cancer Inst 1990;82:208-212.

Vorinostat

Duvic M, Talpur R, Ni X, et al. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). Blood 2007;109:31-39.

Olsen EA, Kim YH, Kuzel TM, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. J Clin Oncol 2007;25:3109-3115.

Duvic M, Olsen EA, Breneman D, et al. Evaluation of the long-term tolerability and clinical benefit of vorinostat in patients with advanced cutaneous T-cell lymphoma. Clin Lymphoma Myeloma 2009;9:412-416.

Romidepsin

Piekarz RL, Frye R, Turner M, et al. Phase II Multi-Institutional Trial of the Histone Deacetylase Inhibitor Romidepsin As Monotherapy for Patients With Cutaneous T-Cell Lymphoma. J Clin Oncol 2009;27:5410-5417.

Whittaker SJ, Demierre MF, Kim EJ, et al. Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. J Clin Oncol 2010; 28:4485-4491.

Extracorporeal photopheresis (ECP)

Edelson R, Berger C, Gasparro F, et al. Treatment of cutaneous T-cell lymphoma by extracorporeal photochemotherapy. Preliminary results. N Engl J Med 1987;316:297-303.

Zic JA, Stricklin GP, Greer JP, et al. Long-term follow-up of patients with cutaneous T-cell lymphoma treated with extracorporeal photochemotherapy. J Am Acad Dermatol 1996;35:935-945.

Zic JA. The treatment of cutaneous T-cell lymphoma with photopheresis. Dermatol Ther 2003;16:337-346.

Methotrexate

Zackheim HS, Kashani-Sabet M, Hwang ST. Low-dose methotrexate to treat erythrodermic cutaneous T-cell lymphoma: results in twenty-nine patients. J Am Acad Dermatol 1996;34:626-631.

Zackheim HS, Kashani-Sabet M, McMillan A. Low-dose methotrexate to treat mycosis fungoides: a retrospective study in 69 patients. J Am Acad Dermatol 2003;49:873-878.

Liposomal doxorubicin

Wollina U, Dummer R, Brockmeyer NH, et al. Multicenter study of pegylated liposomal doxorubicin in patients with cutaneous T-cell lymphoma. Cancer 2003;98:993-1001.

Quereux G, Marques S, Nguyen J-M, et al. Prospective multicenter study of pegylated liposomal doxorubicin treatment in patients with advanced or refractory mycosis fungoides or Sezary syndrome. Arch Dermatol 2008;144:727-733.

Dummer R, Quaglino P, Becker JC, et al. Prospective international multicenter phase II trial of intravenous pegylated liposomal doxorubicin monochemotherapy in patients with stage IIB, IVA, or IVB advanced mycosis fungoides: final results from EORTC 21012. J Clin Oncol 2012;30:4091-4097.

Gemcitabine

Duvic M, Talpur R, Wen S, Kurzrock R, David CL, Apisarnthanarax N. Phase II evaluation of gemcitabine monotherapy for cutaneous T-cell lymphoma. Clin Lymphoma Myeloma 2006;7:51-58.

Marchi E, Alinari L, Tani M, et al. Gemcitabine as frontline treatment for cutaneous T-cell lymphoma: phase II study of 32 patients. Cancer 2005;104:2437-2441.

Zinzani PL, Baliva G, Magagnoli M, et al. Gemcitabine treatment in pretreated cutaneous T-cell lymphoma: experience in 44 patients. J Clin Oncol 2000;18:2603-2606.

Zinzani PL, Venturini F, Stefoni V, et al. Gemcitabine as single agent in pretreated T-cell lymphoma patients: evaluation of the long-term outcome. Ann Oncol 2010;21:860-863.

Awar O, Duvic M. Treatment of transformed mycosis fungoides with intermittent low-dose gemcitabine. Oncology 2007;73:130-135.

Pentostatin

Cummings FJ, Kim K, Neiman RS, et al. Phase II trial of pentostatin in refractory lymphomas and cutaneous T-cell disease. J Clin Oncol 1991;9:565-571.

Greiner D, Olsen EA, Petroni G. Pentostatin (2'-deoxycoformycin) in the treatment of cutaneous T-cell lymphoma. J Am Acad Dermatol 1997;36:950-955.

Tsimberidou AM, Giles F, Duvic M, Fayad L, Kurzrock R. Phase II Study of pentostatin in advanced T-cell lymphoid malignancies. Update on an M.D. Anderson Cancer Center Series. Cancer 2004;100;342-349.

Temozolomide

Tani M, Fina M, Alinari L, Stefoni V, Baccarani M, Zinzani PL. Phase II trial of temozolomide in patients with pretreated cutaneous T-cell lymphoma. Haematologica 2005;90(9):1283-1284.

Querfeld C, Rosen ST, Guitart J, et al. Multicenter phase II trial of temozolomide in mycosis fungoides/ sezary syndrome: correlation with O^6-methylguanine-DNA methyltransferase and mismatch repair proteins. Clin Cancer Res 2011;17:5748-5754.

Pralatrexate

O'Connor OA, Pro B, Pinter-Brown L, et al. Pralatrexate in patients with relapsed or refractory Peripheral T-cell lymphoma: Results from the pivotal PROPEL study. J Clin Oncol 2011;29:1182-1189.

Horwitz SM, Kim YH, Foss F, et al. Identification of an active, well-tolerated dose of pralatrexate in patients with relapsed or refractory cutaneous T-cell lymphoma. Blood 2012;119:4115-4122.

Foss F, Horwitz SM, Coiffier B, et al. Pralatrexate is an effective treatment for relapsed or refractory transformed mycosis fungoides: a subgroup efficacy analysis from the PROPEL study. Clin Lymphoma Myeloma Leuk 2012;12:238-243.

Pembrolizumab

Khodadoust M, Rook A, Porcu P, et al. Pembrolizumab for treatment of relapsed/ refractory mycosis fungoides and Sezary syndrome: Clinical efficacy in a CITN multicenter phase 2 study [abstract]. Blood 2018;125:Abstract 181.

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SUGGESTED TREATMENT REGIMENS
References

Combination Therapies

Skin-directed + Systemic

Rupoli S, Goteri G, Pulini S, et al. Long term experience with low dose interferon alpha and PUVA in the management of early mycosis fungoides. Eur J Haematol 2005;75:136-145.

Kuzel T, Roenigk H Jr, Samuelson E, et al. Effectiveness of interferon alfa-2a combined with phototherapy for mycosis fungoides and the Sézary syndrome. J Clin Oncol 1995;13:257-263.

McGinnis K, Shapiro M, Vittorio C, et al. Psoralen plus long wave UV A (PUVA) and bexarotene therapy: An effective and synergistic combined adjunct to therapy for patients with advanced cutaneous T cell lymphoma. Arch Dermatol 2003;139:771-775.

Wilson LD, Jones GW, Kim D, et al. Experience with total skin electron beam therapy in combination with extracorporeal photopheresis in the management of patients with erythrodermic (T4) mycosis fungoides. J Am Acad Dermatol 2000;43:54-60.

Stadler R, Otte H-G, Luger T, et al. Prospective randomized multicenter clinical trial on the use of interferon alpha -2a plus acitretin versus interferon alpha -2a plus PUVA in patients with cutaneous T-cell lymphoma stages I and II. Blood 1998;92:3578-3581.

Systemic + Systemic

Straus DJ, Duvic M, Kuzel T, et al. Results of a phase II trial of oral bexarotene (Targretin) combined with interferon alfa 2b (Intron A) for patients with cutaneous T cell lymphoma. Cancer 2007;109:1799-1803.

Talpur R, Ward S, Apisarnthanarax N, Breuer Mcham J, Duvic M. Optimizing bexarotene therapy for cutaneous T cell lymphoma. J Am Acad Dermatol 2002;47:672-684.

Suchin KR, Cucchiara AJ, Gottleib SL, et al. Treatment of cutaneous T-cell lymphoma with combined immunomodulatory therapy: a 14-year experience at a single institution. Arch Dermatol. 2002;138:1054-1060.

Raphael BA, Shin DB, Suchin KR, et al. High clinical response rate of Sezary syndrome to immunomodulatory therapies: prognostic markers of response. Arch Dermatol 2011;147:1410-1415.

Allogeneic hematopoietic cell transplant

de Masson A, Beylot-Barry M, Bouaziz J, et al. Allogeneic stem cell transplantation for advanced cutaneous T-cell lymphomas: a study from the French Society of Bone Marrow Transplantation and French Study Group on Cutaneous Lymphomas. Haematologica 2014;99:527-534.

Duarte R, Boumendil A, Onida F, et al. Long-term outcome of allogeneic hematopoietic cell transplantation for patients with mycosis fungoides and Sézary syndrome: a European society for blood and marrow transplantation lymphoma working party extended analysis. J Clin Oncol 2014;32:3347-3348.

Duarte RF, Schmitz N, Servitje O, Sureda A. Haematopoietic stem cell transplantation for patients with primary cutaneous T-cell lymphoma. Bone Marrow Transplant 2008;41:597-604.

Hosing C, Bassett R, Dabaja B, et al. Allogeneic stem-cell transplantation in patients with cutaneous lymphoma: updated results from a single institution. Ann Oncol 2015;26:2490-2495.

Lechowicz M, Lazarus H, Carreras J, et al. Allogeneic hematopoietic cell transplantation for mycosis fungoides and Sezary syndrome. Bone Marrow Transplant 2014;49:1360-1365.

Wu PA, Kim YH, Lavori PW, Hoppe RT, Stockerl-Goldstein KE. A meta-analysis of patients receiving allogeneic or autologous hematopoietic stem cell transplant in mycosis fungoides and Sezary syndrome. Biol Blood Marrow Transplant 2009;15:982-990.

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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[1]**
      - – **Doxepin[1]**
      - – **Gabapentin[2,3]**
    - ◊ **Second-line**
      - – **Aprepitant[4,5]**
      - – **Mirtazapine[6]**
      - – **Selective serotonin reuptake inhibitors[7]**
    - ◊ **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, nares, or other cultures for Staphylococcus aureus (S. aureus) infection or colonization**
    - ◊ **Intranasal mupirocin**
    - ◊ **Oral dicloxacillin or cephalexin**
    - ◊ **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.**

[1]Eschler D, Klein PA. An evidence-based review of the efficacy of topical antihistamines in the relief of pruritus. J Drugs Dermatol 2010;9:992-997.
[2]Matsuda KM, Sharma D, Schonfeld AR, Kwatra SG. Gabapentin and pregabalin for the treatment of chronic pruritus. J Am Acad Dermatol 2018;75:619-625.
[3]Demierre MF, Taverna J. Mirtazapine and gabapentin for reducing pruritus in cutaneous T-cell lymphoma. Am Acad Dermatol 2006;55:543-544.
[4]Jiménez Gallo D, Albarrán Planelles C, Linares Barrios M, et al. Treatment of pruritus in early-stage hypopigmented mycosis fungoides with aprepitant. Dermatol Ther 2014;27:178-182.
[5]Duval A, Dubertret L. Aprepitant as an antipruritic agent? N Engl J Med 2009;361:1415-1416.
[6]Demierre M, Taverna J. Mirtazapine and gabapentin for reducing pruritus in cutaneous T-cell lymphoma. Am Acad Dermatol 2006;55:543-544.
[7]Ständer S1, Böckenholt B, Schürmeyer-Horst F, et al. Treatment of chronic pruritus with the selective serotonin re-uptake inhibitors paroxetine and fluvoxamine: results of an open-labelled, two-arm proof-of-concept study. Acta Derm Venereol 2009;89:45-51.

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PRINCIPLES OF RADIATION THERAPY FOR MF/SS

- **Treatment of individual plaques or tumors**
  - **Optimal management for individual plaque and tumor lesions is with external beam RT, 8–12 Gy; 24 to 30 Gy for unilesional presentation. 8 Gy may be given in a single fraction.**
  - **Surface margins beyond area of clinically evident disease will vary depending on lesion size and body site and must take into account dosimetry of the beam being used. Surface margins of 1.0–1.5 cm are generally adequate.**
  - **Margins in depth should include the volume at risk for involvement.**
  - **Generally, treatment with 6–9 MeV electrons (with surface bolus) provides an adequate depth of treatment. Alternatively, low energy x-rays (~100 Kv) may be used.**
  - **For certain body surfaces, higher-energy photon fields and opposed-field treatment (with bolus) may be required.**

- **Total Skin Electron Beam Therapy (TSEBT)**
  - **A variety of techniques may be utilized to cover the entire cutaneous surface. Patients are generally treated in the standing position on a rotating platform or with multiple body positions to ensure total skin coverage.**
  - **The dose range is 12–36 Gy, generally 4-6 Gy per week. The advantage of lower total dose includes fewer short-term complications and better ability to re-treat for progressive disease.**
  - **“Shadowed” areas may need to be supplemented with individual electron fields.**
  - **Individual tumors may be boosted with doses of 4–12 Gy.**

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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)

[a]Ralfkiaer E, Willemze R, Paulli M, Kadin ME. Primary cutaneous CD30-positive T-cell lymphoproliferative disorders. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:300-301.
[b]Swerdlow SH, Campo E, Pileri SA, et al. The 2018 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2018;127:2375-2390.
[c]Benner MF, Willemze R. Applicability and prognostic value of the new TNM classification system in 135 patients with primary cutaneous anaplastic large cell lymphoma. Arch Dermatol 2009;145:1399-1404.
[d]Kempf W, Pfaltz K, Vermeer MH, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Blood 2011;118:4024-4035.
[e]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.)

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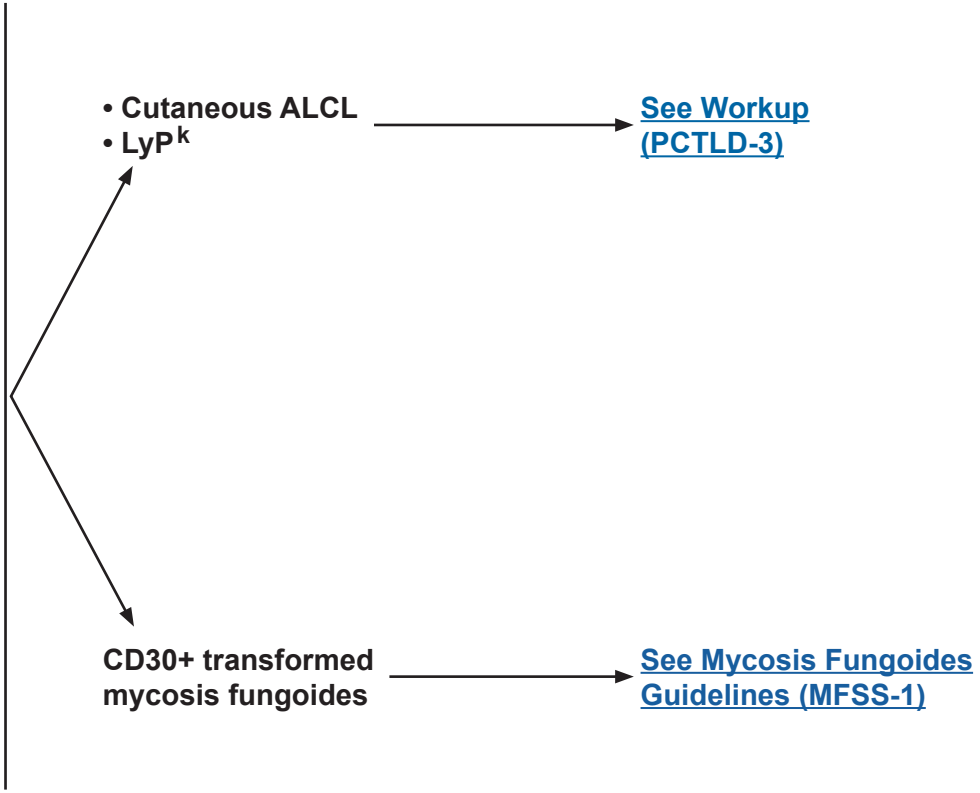
DIAGNOSIS

ESSENTIAL:

- Clinical presentation: see Overview and Definition
- Clinical pathologic correlation is essential
- Complete skin examination for evidence of MF
- Biopsy of suspicious skin sites
  - 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 (punch, incisional, or excisional) of clinical lesions present will aid in final diagnosis.
- Adequate immunophenotyping to establish diagnosis[f,g] on skin biopsy:
  - IHC: CD3, CD4, CD8, CD20, CD30, CD56, ALK[h]

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- On skin biopsy, expanded IHC: CD2, CD5, CD7, CD25, TIA1, granzyme B, perforin, GM1, EBER-ISH, IRF4/MUM1, EMA
- Molecular analysis to detect clonal T-cell antigen receptor (TCR)[i] gene rearrangements (TCR beta, TCR gamma) or other assessment of clonality[j]
- FISH: *DUSP22* gene rearrangement
- Excisional or incisional biopsy of suspicious lymph nodes
- Assessment of HTLV-1 serology in at-risk populations to identify CD30+ ATLL



[f]See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (See B-cell Lymphomas Guidelines).
[g]Typical immunophenotype: CD30+ (>75% cells), CD4+ variable loss of CD2/CD5/CD3, CD8+ (<5%) cytotoxic granule proteins positive.
[h]ALK positivity and t(2;5) translocation is typically absent in PC-ALCL and LyP.
[i]TCR clonal 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 CTCL. Demonstration of identical clones in skin, blood, and/or lymph node may be helpful in selected cases.
[j]Such as FISH, karyotype, genomic analysis.
[k]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.

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WORKUP

Cutaneous ALCL →

ESSENTIAL:
- History and complete physical examination including complete skin examination;[l] palpation of peripheral lymph node regions; liver or spleen enlargement
- CBC with differential
- Comprehensive metabolic panel
- LDH
- C/A/P CT with contrast or integrated whole body PET/CT
- Biopsy suspicious nodes[e,m,n]
- Bone marrow aspiration and biopsy optional for solitary C-ALCL or C-ALCL without if extracutaneous involvement

USEFUL IN SELECTED CASES:
- Pregnancy testing in women of child-bearing age[o]

→ Primary cutaneous ALCL → **See Primary Treatment (PCTLD-4)**

→ Cutaneous ALCL with regional node → **See Primary Treatment (PCTLD-4)**

→ Systemic ALCL → **See Peripheral T-cell Lymphoma (TCEL-1)**

LyP[k] →

ESSENTIAL:
- History and complete physical examination including complete skim examination;[l] palpation of peripheral lymph node regions; liver or spleen enlargement
- CBC with differential
- Comprehensive metabolic panel
- LDH

USEFUL IN SELECTED CASES:
- Pregnancy testing in women of child-bearing age[o]
- C/A/P CT with contrast or integrated whole body PET/CT[k,p]
- Bone marrow aspiration and biopsy (not done for typical LyP)[k,p]

→ **See Primary Treatment for LyP (PCTLD-5)**

[e]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.)
[k]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.
[l]Monitoring the size and number of lesions will assist with response assessment.
[m]Consider systemic ALCL, regional lymph node involvement with PC-ALCL, or lymph node involvement with transformed MF.
[n]Consider PC-ALCL if in draining lymph nodes only.
[o]Many skin-directed and systemic therapies are contraindicated or of unknown safety in pregnancy. Refer to individual drug information.
[p]Only done to exclude an associated lymphoma.

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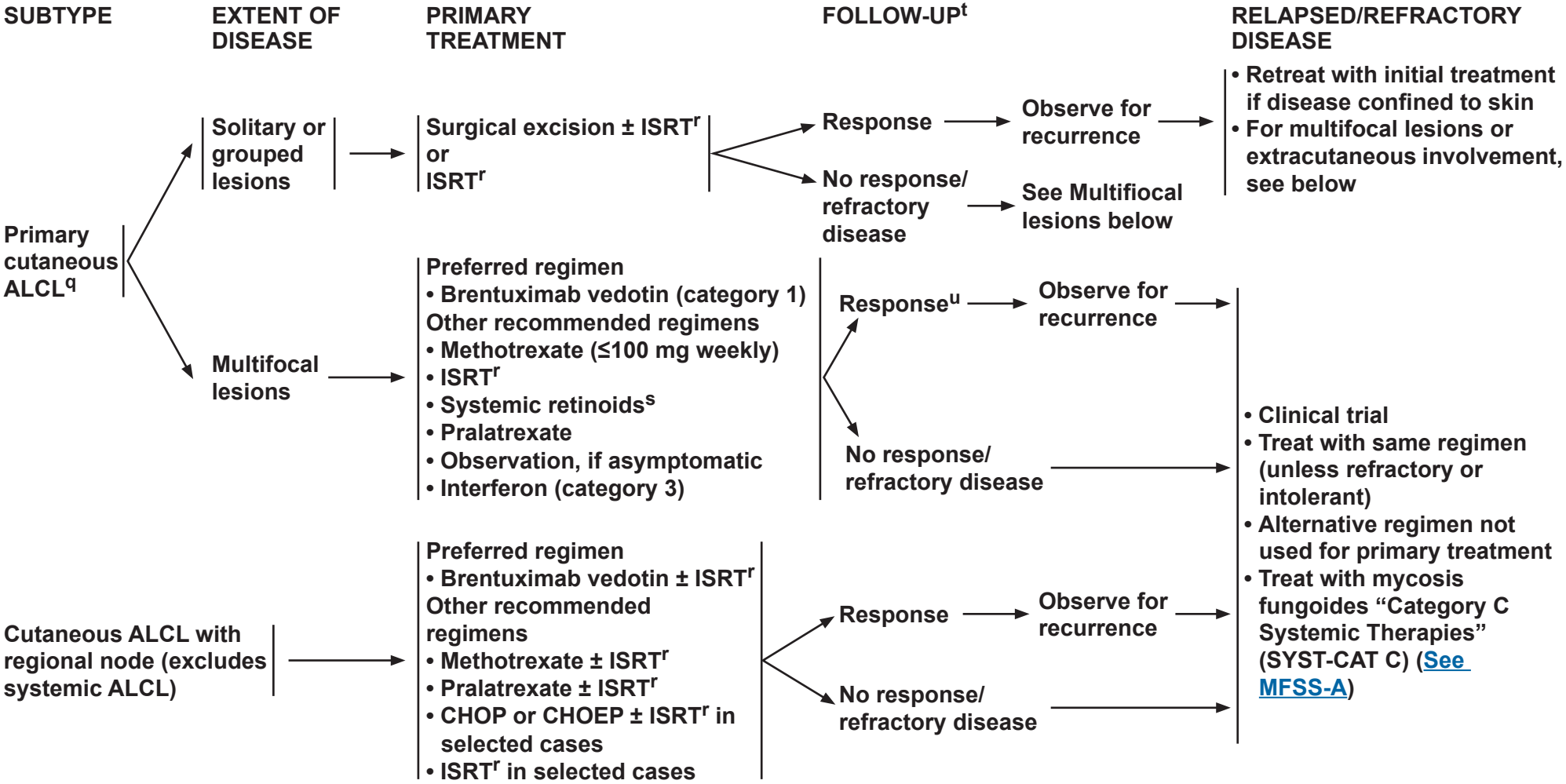

[q]Regression of lesions may occur in up to 44% of cases.
[r]See Principles of Radiation Therapy (LYMP-C).
[s]Limited data from case reports (eg, bexarotene).
[t]Mycosis fungoides can develop over time; continue to conduct thorough skin exam during follow-up.
[u]Patients with cutaneous disease achieving 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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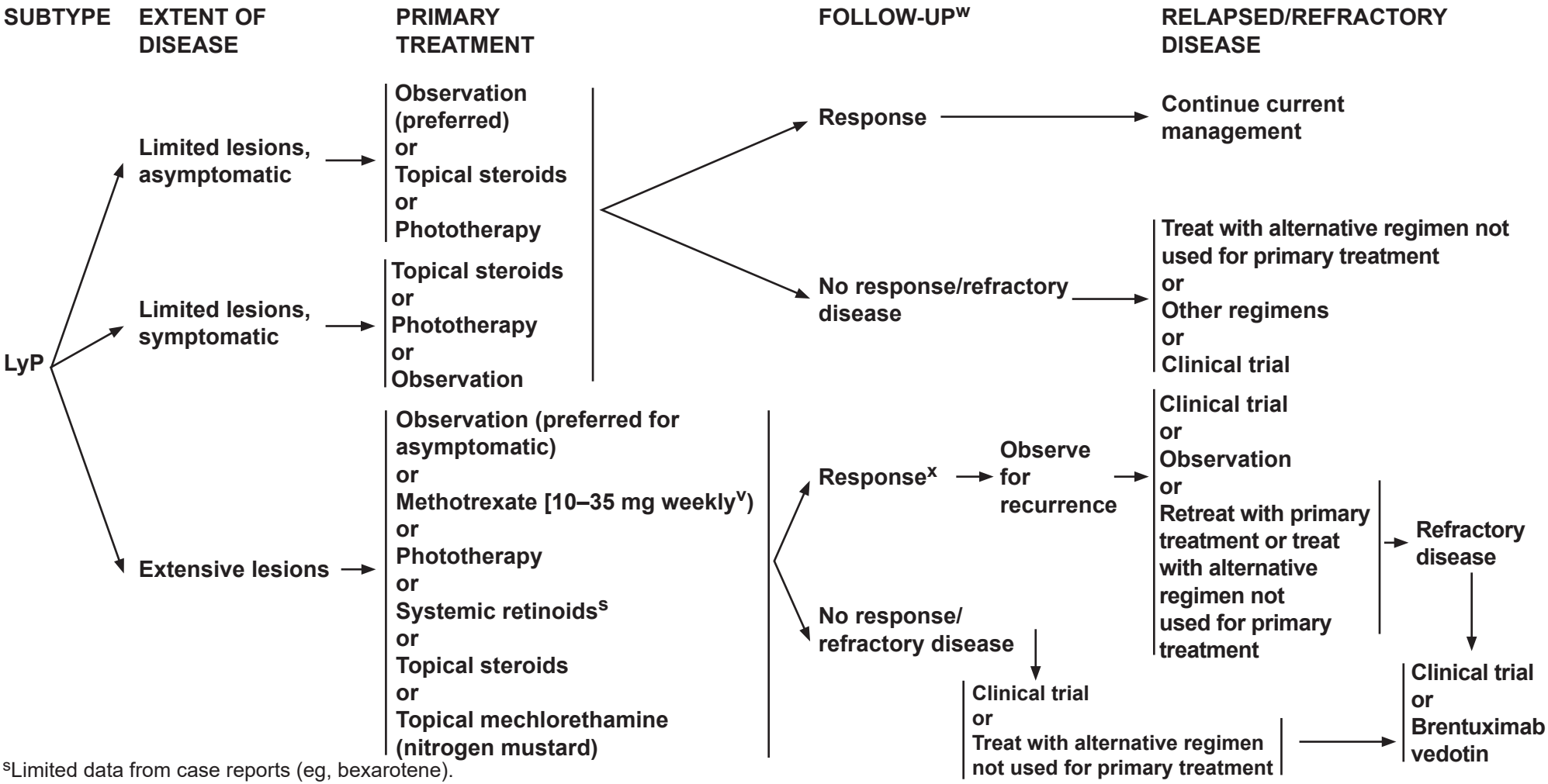

[s]Limited data from case reports (eg, bexarotene).

[v]Kempf W, Pfaltz K, Vermeer MH, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Blood 2011;118:4024-4035.

[w]Life-long follow-up is warranted due to high risks for second lymphoid malignancies; continue to conduct thorough skin exam during follow-up.

[x]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 responds 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.
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

General approach/overview of management

Kempf W, Pfaltz K, Vermeer MH, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30+ lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma. Blood 2011;118:4024-4035.

Vergier B, Beylot-Barry M, Pulford K, et al. Statistical evaluation of diagnostic and prognostic features of CD30+ cutaneous lymphoproliferative disorders: a clinicopathologic study of 65 cases. Am J Surg Pathol 1998;22:1192-1202.

Liu HL, Hoppe RT, Kohler S, et al. CD30+ cutaneous lymphoproliferative disorders: the Stanford experience in lymphomatoid papulosos and primary cutaneous anaplastic large cell lymphoma. J Am Acad Dermatol 2003;49:1049-1058.

Woo DK, Jones CR, Vanoli-Stolz MN, et al. Prognostic factors in primary cutaneous anaplastic large cell lymphoma: characterization of clinical subset with worse outcome. Arch Dermatol 2009;145:667-674.

Skin-directed therapies

Topical steroids

Paul MA, Krowchuk DP, Hitchcock MG, et al. Lymphomatoid papulosis: successful weekly pulse superpotent topical corticosteroid therapy in three pediatric patients. Pediatr Dermatol 1996;13:501-506.

Phototherapy

Wantzin GL, Thomsen K. PUVA-treatment in lymphomatoid papulosis. Br J Dermatol 1982;107:687-690.

Topical nitrogen mustard

Vonderheid EC, Tan ET, Kantor AF, et al. Long-term efficacy, curative potential, and carcinogenicity of topical mechloethamine chemotherapy in cutaneous T cell lymphoma. J Am Acad Dermatol 1989;20:416-428.

Radiation therapy

Yu JB, McNiff JM, Lund MW, et al. Treatment of primary cutaneous CD30+ anaplastic large cell lymphoma with radiation therapy. Int J Radiat Oncol Biol Phys 2008;70:1542-1545.

Systemic therapies

Methotrexate

Everett MA. Treatment of lymphomatoid papulosis with methotrexate. Br J Dermatol 1984;111:631.

Vonderheid EC, Sajjadian A, Kaden ME. Methotrexate is effective for lymphomatoid papulosis and other primary cutaneous CD30+ lymphoproliferative disorders. J Am Acad Dermatol 1996;34:470-481.

Fujita H, Nagatani T, Miyazawa M et al. Primary cutaneous anaplastic large cell lymphoma successfully treated with low-dose methotrexate. Eur J Dermatol 2008;18:360-361.

Systemic therapies (Continued)

Pralatrexate

Horwitz SM, Kim YH, Foss F, et al. Identification of an active, well-tolerated dose of pralatrexate in patients with relapsed or refractory cutaneous T cell lymphoma. Blood 2012;119:4115-4122.

Systemic retinoids

Nakamura S, Hashimoto Y, Nishi K, et al. Primary cutaneous CD30+ lymphoproliferative disorder successfully treated with etretinate. Eur J Dermatol 2012;22:709-710.

Krathen RA, Ward S, Duvic M. Bexarotene is a new treatment option for lymphomatoid papulosis. Dermatology 2003;206:142-147.

Wyss M, Dummer R, Dommann SN, et al. Lymphomatoid papulosis: treatment with recombinant interferon alfa-2a and etretinate. Dermatology 1995;190:288-291.

Sheehy JM, Catherwood M, Pettengeil R, et al. Sustained response of primary cutaneous CD30+ anaplastic large cell lymphoma to bexarotene and photopheresis. Leuk Lymphoma 2009;50:1389-1391.

Interferons

Proctor SJ, Jackson GH, Lennard AL, et al. Lymphotoid papulosis: response to treatment with recombinant interferon alfa-2b. J Clin Oncol 1992;10:170.

Yagi H, Tokura Y, Furukawa F, et al. Th2 cytokine mRNA expression in primary cutaneous CD30+ lymphoproliferative disorders: successful treatment with recombinant interferon-gamma. J Invest Dermatol 1996;107:827-832.

Schmuch M, Topar G, Illersperger B, et al. Therapeutic use of interferon-alpha for lymphomatoid papulosis. Cancer 2000;89:1603-1610.

Brentuximab vedotin

Duvic M, Tetzlaff MT, Gangar P, et al. Results of a phase II trial of brentuximab vedotin for CD30+ cutaneous T-cell lymphoma and lymphomatoid papulosis. J Clin Oncol 2015; 33:3759-65.

Broccoli A, Derenzini E, Pellegrini C, et al. Complete response of relapsed systemic and cutaneous anaplastic large cell lymphoma using brentuximab vedotin: 2 case reports. Clin Lymphoma Myeloma Leuk 2013;13:493-495.

Mody K, Wallace JS, Stearns DM, et al. CD30+ cutaneous T cell lymphoma and response to brentuximab vedotin: 2 illustrative cases. Clin Lymphoma Myeloma Leuk 2014;13:319-323.

Desai A, Telang GH, Olszewski AJ. Remission of primary cutaneous anaplastic large cell lymphoma after a brief course of brentuximab vedotin. Ann Hematol 2013;92:567-568.

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T-cell Large Granular Lymphocytic Leukemia

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DIAGNOSIS[a]

ESSENTIAL:[b,c]
- 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
- Adequate immunophenotyping to establish diagnosis[d]
  - Cell surface marker analysis by flow cytometry: CD3, CD4, CD5, CD7, CD8, CD16, CD56, CD57, CD28, TCRαß, TCRγδ, CD45RA, CD62L with or without
  - IHC panel: CD3, CD4, CD5, CD7, CD8, CD56, CD57, TCRbeta, TCRgamma, TIA1, perforin, granzyme B

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- Bone marrow aspirate and biopsy[e]
- Mutational analysis: *STAT3* and *STAT5B*
- Molecular analysis to detect clonal T-cell antigen receptor (TCR) gene rearrangements[f] or other assessment of clonality[g]
- 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[b] (especially rheumatoid arthritis [RA])
- Performance status
- CBC with differential
- Comprehensive metabolic panel
- Serologic studies: HIV-1,2; HTLV-1,2 for at-risk populations
- 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[h]

See Indication for Treatment (LGLL-2)

[a]Approximately 10% of LGLL will be of the NK, provisional type called *chronic lymphoproliferative disorder of NK-cells*. This is treated with a similar approach to T-LGL.

[b]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.

[c]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.

[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]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.

[f]TCR clonal gene rearrangement results should be interpreted with caution. TCR clonal 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.

[g]Such as FISH, karyotype, genomic analysis.

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

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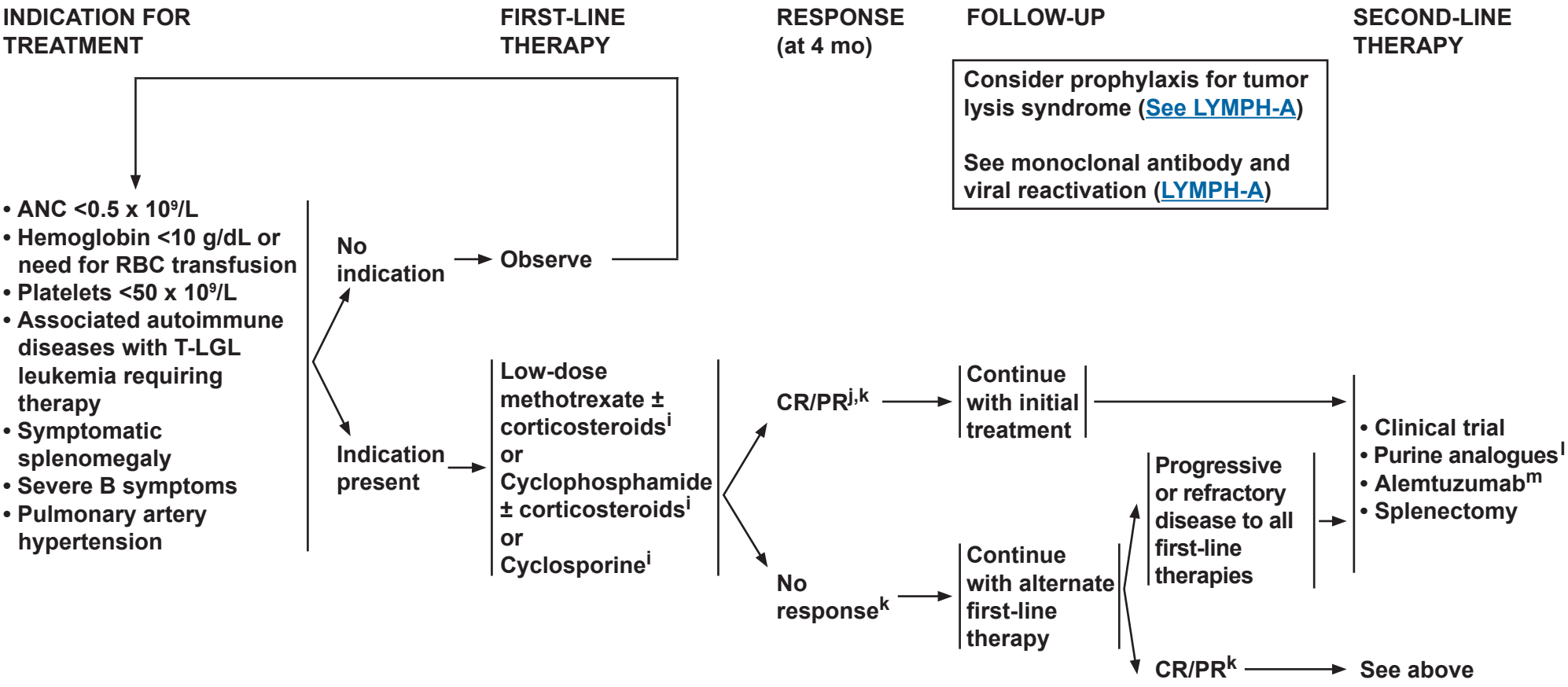

[i]Methotrexate with or without steroids may be beneficial in patients with autoimmune disease; cyclophosphamide or cyclosporine may be used as a first- or second-line option in patients with anemia. Lamy T, Loughran TP Jr. How I treat LGL leukemia. Blood 2011;117(10):2764-74.

[j]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. Bareau B, Rey J, Hamidou M, et al. Analysis of a French cohort of patients with large granular lymphocyte leukemia: a report on 229 cases. Hematologica 2010;95:1534-1541.

[k]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.

[l]Pentostatin, cladribine, and fludarabine have been used in LGL.

[m]While alemtuzumab is no longer commercially available, it may be obtained for clinical use.

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DIAGNOSIS

ESSENTIAL:[a]
- **CBC with differential and peripheral blood smear for atypical cells:[c] lymphocytosis (ALC >4000/µL in adults) in acute and chronic subtypes[d]**
- **Flow cytometry on peripheral blood[e]**
- **HTLV-1 serology:[b] 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[f] 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:[g,h] CD3, CD4, CD5, CD7, CD8, CD25, CD30**

WORKUP

ESSENTIAL:
- **History and physical examination, including complete skin exam**
- **Comprehensive metabolic panel**
- **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**
- **Uric acid**

DIAGNOSTIC CATEGORY[d]

- **See First-Line Therapy for Chronic/ Smoldering Subtype (ATLL-2)**
- **See First-Line Therapy for Acute Subtype (ATLL-3)**
- **See First-Line Therapy for Lymphoma (ATLL-3)**

[a]The diagnosis of ATLL requires histopathology and immunophenotyping of tumor lesion, or morphology and immunophenotying of peripheral blood, *and* HTLV-1 serology.

[b]See map for prevalence of HTLV-1 by geographic region.

[c]Typical ATL cells ("flower cells") have distinctly polylobated nuclei with homogeneous and condensed chromatin, small or absent nucleoli, and agranular and basophilic cytoplasm, but multiple 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.

[d]Shimoyama M and members of The Lymphoma Study Group. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the Lymphoma Study Group (1984-87). Br J Haematol 1991;79:428-437.

[e]Typical 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.

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

[g]See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (See B-cell Lymphomas Guidelines)

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

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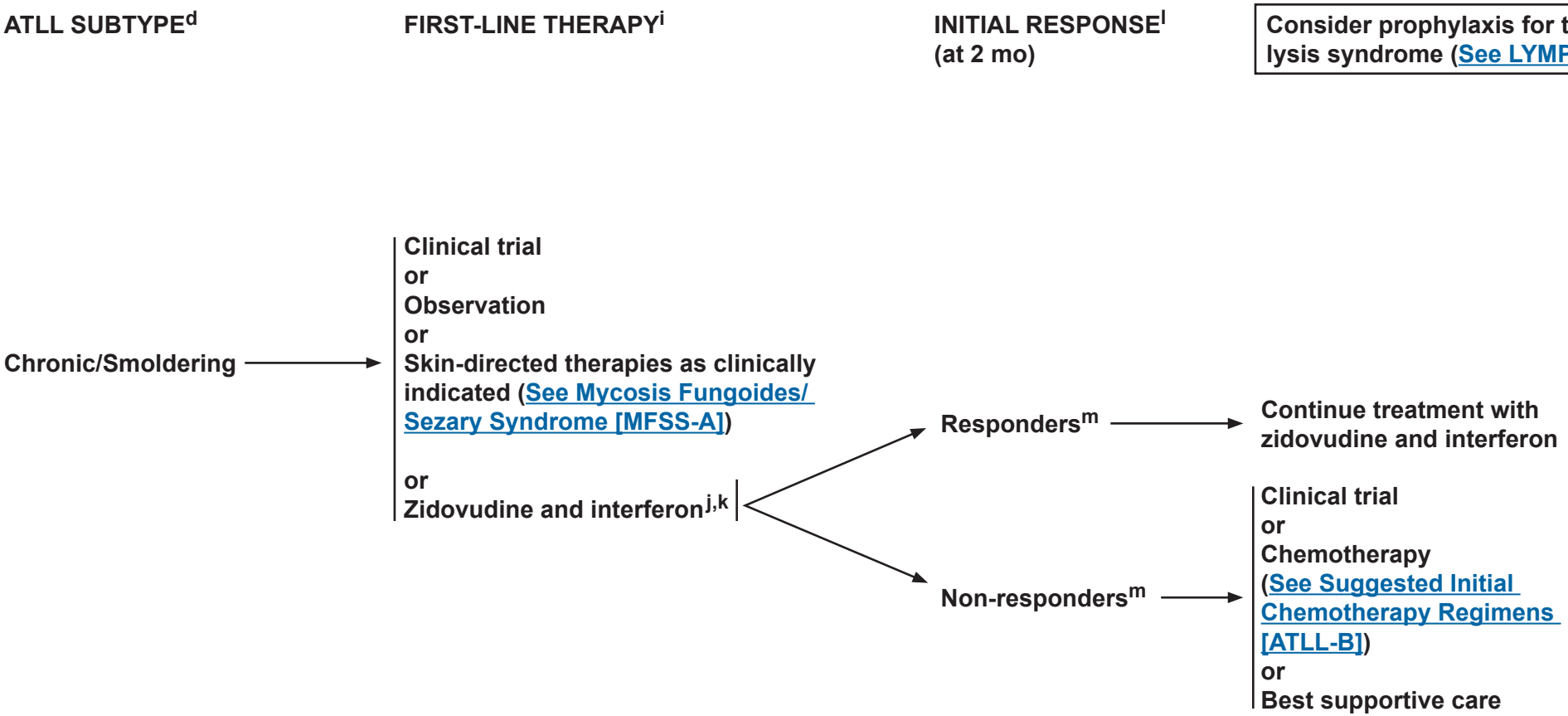

[d]Shimoyama M and members of The Lymphoma Study Group. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the Lymphoma Study Group (1984-87). Br J Haematol 1991;79:428-437.
[i]Anti-infective prophylaxis: Pneumocystis jirovecii pneumonia (PJP) prophylaxis with sulfamethoxazole/trimethoprim or equivalent; Screening and treatment (if needed) for strongyloidiasis.
[j]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.
[k]See references for zidovudine and interferon (ATLL-C).
[l]If nodal disease is present, repeat C/A/P CT with contrast or PET/CT.
[m]See Response Criteria for ATLL (ATLL-A). Responders include CR, uncertified PR, and PR.

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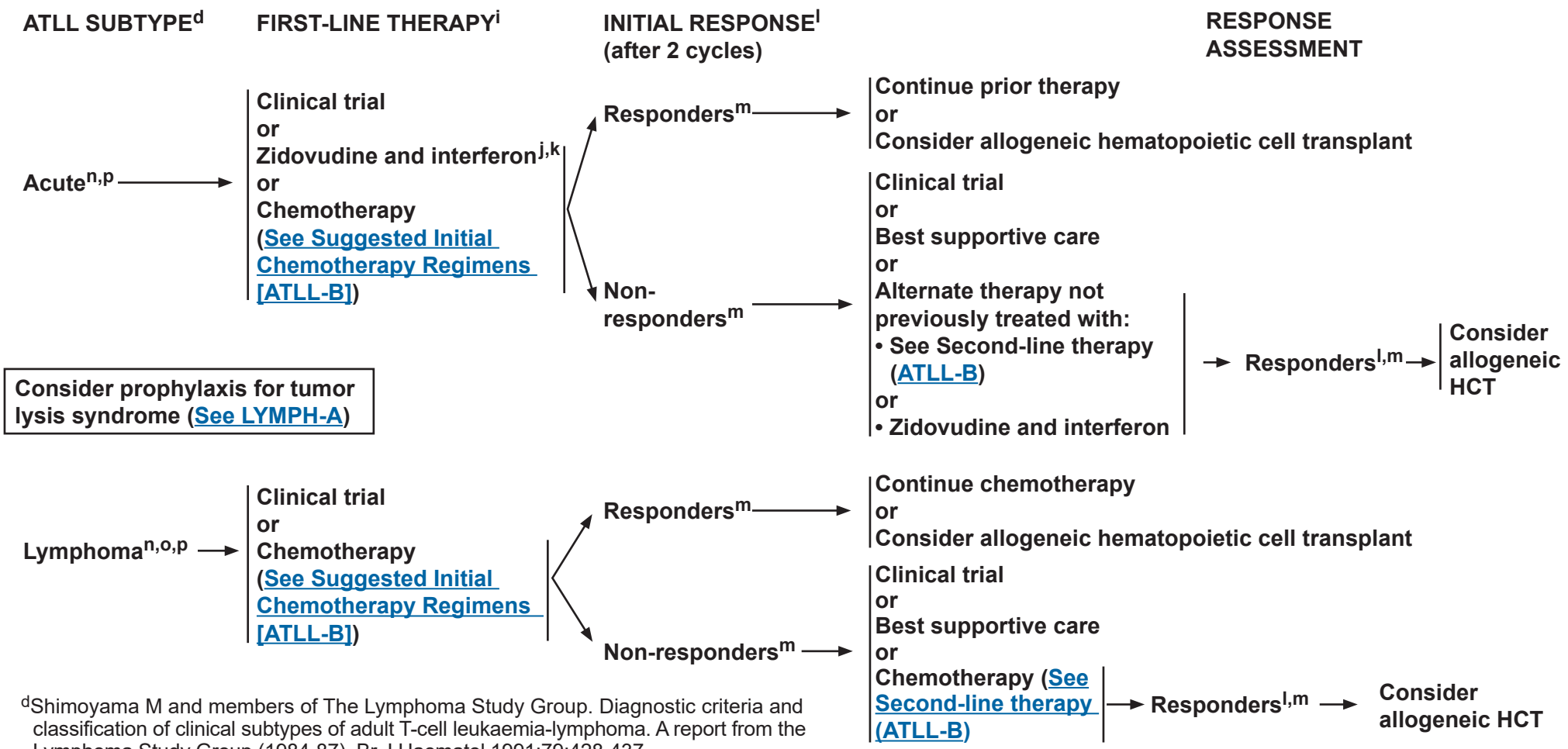

[d]Shimoyama M and members of The Lymphoma Study Group. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the Lymphoma Study Group (1984-87). Br J Haematol 1991;79:428-437.

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

[j]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.

[k]See references for zidovudine and interferon (ATLL-C).

[l]If nodal disease is present, repeat C/A/P CT with contrast or PET/CT.

[m]See Response Criteria for ATLL (ATLL-A). Responders include CR, uncertified PR, and PR.

[n]Efficacy of long-term treatment is limited. There are small series where transplant is beneficial. There is no defined treatment.

[o]Antiviral therapy is not effective.

[p]CNS prophylaxis is strongly recommended.

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RESPONSE CRITERIA FOR ATLL[a]

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

*Required that each criterion 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 $<4 \times 10^9$/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 $>4 \times 10^9$/L.

[a]Tsukasaki K, Hermine O, Bazarbachi A, et al. Definition, prognostic factors, treatment, and response criteria of adult T-cell leukemia-lymphoma: A proposal from an international consensus meeting. J Clin Oncol 2009;27:453-459.

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SUGGESTED TREATMENT REGIMENS
(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

Alduaij A, Butera JN, Treaba D, Castillo J. Complete remission in two cases of adult T-cell leukemia/lymphoma treated with hyper-CVAD: a case report and review of the literature. Clin Lymphoma Myeloma Leuk 2010;10:480-483.

Ratner L, Harrington W, Feng X, et al. Human T-cell leukemia virus reactivation with progression of adult T-cell leukemia-lymphoma. PLoS ONE 2009;4:e4420.

Tsukasaki K, Utsunomiya A, Fukuda H, et al. VCAP-AMP-VECP compared with biweekly CHOP for adult T-cell leukemia-lymphoma: Japan Clinical Oncology Group Study JCOG9801. J Clin Oncol 2007;25:5458-5464.

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REFERENCES FOR ZIDOVUDINE AND INTERFERON

Zidovudine and interferon

Bazarbachi A, Hermine O. Treatment with a combination of zidovudine and alpha-interferon in naive and pretreated adult T-cell leukemia/lymphoma patients. J Acquir Immune Defic Syndr Hum Retrovirol 1996;13 Suppl 1:S186-190.

Bazarbachi A, Plumelle Y, Carlos Ramos J, et al. Meta-analysis on the use of zidovudine and interferon-alfa in adult T-cell leukemia/lymphoma showing improved survival in the leukemic subtypes. J Clin Oncol 2010;28:4177-4183.

Hermine O, Allard I, Levy V, Arnulf B, Gessain A, Bazarbachi A. A prospective phase II clinical trial with the use of zidovudine and interferon-alpha in the acute and lymphoma forms of adult T-cell leukemia/lymphoma. Hematol J 2002;3:276-282.

Hodson A, Crichton S, Montoto S, et al. Use of zidovudine and interferon alfa with chemotherapy improves survival in both acute and lymphoma subtypes of adult T-cell leukemia/lymphoma. J Clin Oncol 2011;29:4696-4701.

White JD, Wharfe G, Stewart DM, et al. The combination of zidovudine and interferon alpha-2B in the treatment of adult T-cell leukemia/lymphoma. Leuk Lymphoma 2001;40:287-294.

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T-Cell Prolymphocytic Leukemia

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DIAGNOSIS

ESSENTIAL:
- Tissue histology not essential for diagnosis
- Peripheral blood smear analysis for morphology
- Peripheral blood flow cytometry to establish diagnosis[a]
  - TdT, CD 1a, CD2, CD3, CD4, CD5, CD7, CD8, CD52, TCRalpha, TCRbeta
- 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 clonal T-cell antigen receptor (TCR) gene rearrangements[b] or other assessment of clonality[c]
- IHC: TCL1
- Bone marrow biopsy
  - IHC panel: CD1a, TdT, CD2, CD3, CD5, TCL1

WORKUP

ESSENTIAL:
- History and physical examination, including complete skin exam, and evaluation of lymph nodes, spleen, and liver.
- Performance status
- LDH
- CBC with differential
- Comprehensive metabolic panel
- 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

→ Asymptomatic[d] → Observe until progression or symptomatic

→ Symptomatic disease → See TPLL-2

[a]Typical immunophenotype: CD1a-, TdT-, CD2+, sCD3+/-, cCD3+/-, CD5+, CD7++, CD52++, TCRαß+, CD4+/CD8- (65%), CD4+/CD8+ (21%), CD4-/CD8+ (13%).
[b]TCR clonal gene rearrangement results should be interpreted with caution. TCR clonal gene rearrangement can be seen in non-malignant conditions or may not be demonstrated in all cases of CTCL. Demonstration of identical clones in skin, blood, and/or lymph node may be helpful in selected cases.
[c]Such as FISH, karyotype, genomic analysis.
[d]In a minority of patients, the disease may be asymptomatic and can follow an indolent course of variable duration. In these selected cases expectant observation is a reasonable option.

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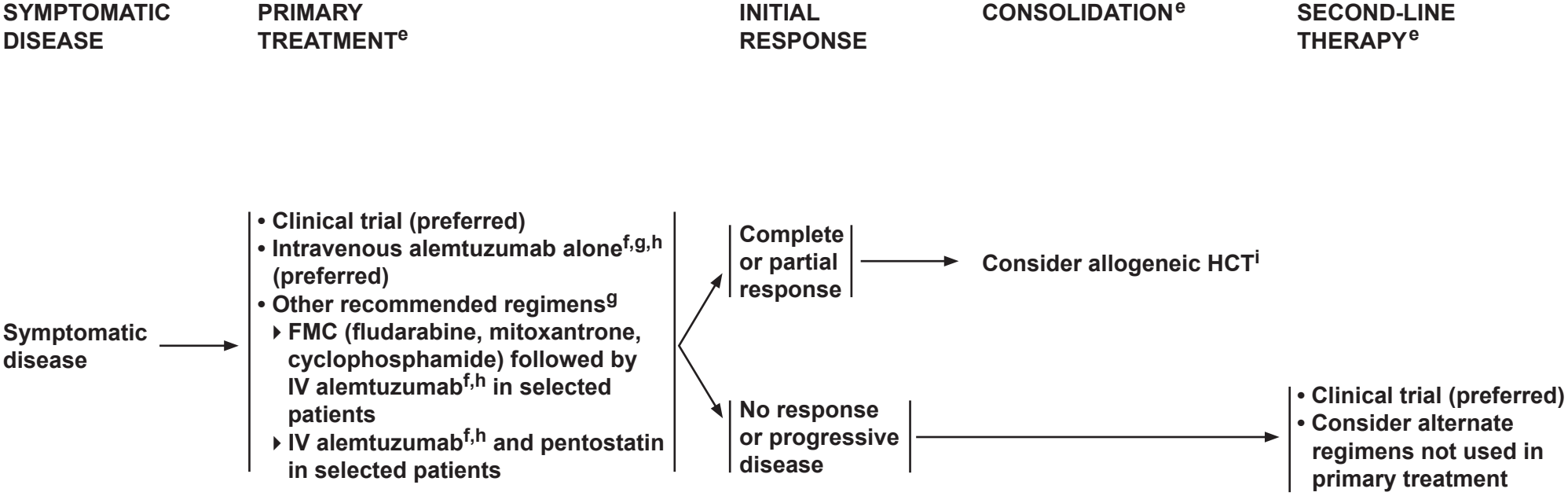

Consider prophylaxis for tumor lysis syndrome (See LYMPH-A)

See monoclonal antibody and viral reactivation (LYMPH-A)

[e]See Treatment References (TPLL-A).
[f]IV alemtuzumab is preferred over subcutaneous based on data showing inferior activity with subcutaneous delivery in patients with T-PLL (Dearden CE, Khot A, Else M, et al. Alemtuzumab therapy in T-cell prolymphocytic leukaemia: Comparing efficacy in a series treated intravenously and a study piloting the subcutaneous route. Blood 2011;118:5799-5802).
[g]Monitor for CMV reactivation; anti-infective prophylaxis for herpes virus and PCP is recommended when treating with alemtuzumab ± purine analogs.
[h]While alemtuzumab is no longer commercially available, it may be obtained for clinical use.
[i]Consider HDT/ASCR if a suitable donor is not available.

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TREATMENT REFERENCES

Alemtuzumab

Dearden CE, Matutes E, Cazin B, et al. High remission rate in T-cell prolymphocytic leukemia with CAMPATH-1H. Blood 2001;98:1721-1726.

Keating MJ, Cazin B, Coutre S, et al. Campath-1H treatment of T-cell prolymphocytic leukemia in patients for whom at least one prior chemotherapy regimen has failed. J Clin Oncol 2002;20:205-213.

Dearden CE, Khot A, Else M, et al. Alemtuzumab therapy in T-cell prolymphocytic leukaemia: Comparing efficacy in a series treated intravenously and a study piloting the subcutaneous route. Blood 2011;118:5799-5802.

Alemtuzumab + pentostatin

Ravandi F, Aribi A, O'Brien S, et al. Phase II study of alemtuzumab in combination with pentostatin in patients with T-cell neoplasms. J Clin Oncol 2009;27:5425-5430.

FMC (fludarabine, mitoxantrone, cyclophosphamide) followed by alemtuzumab

Hopfinger G, Busch R, Pflug N, et al. Sequential chemoimmunotherapy of fludarabine, mitoxantrone, and cyclophosphamide induction followed by alemtuzumab consolidation is effective in T-cell prolymphocytic leukemia. Cancer 2013;119:2258-2267.

Allogeneic hematopoietic cell transplant

Castagna L, Nozza A, Bertuzzi A, et al. Allogeneic peripheral blood stem cell transplantation with reduced intensity conditioning in primary refractory prolymphocytic leukemia: graft-versus-leukemia effect without graft-versus-host disease. Bone Marrow Transplant 2001;28:1155-1156.

Kalaycio ME, Kukreja M, Woolfrey AE, et al. Allogeneic hematopoietic cell transplant for prolymphocytic leukemia. Biol Blood Marrow Transplant. 2010;16:543-547.

Murase K, Matsunaga T, Sato T, et al. Allogeneic bone marrow transplantation in a patient with T-prolymphocytic leukemia with small-intestinal involvement. Int J Clin Oncol 2003;8:391-394.

Wiktor-Jedrzejczak W, Dearden C, de Wreede L, et al. Hematopoietic stem cell transplantation in T-prolymphocytic leukemia: A retrospective study from the European Group for Blood and Marrow Transplantation and the Royal Marsden Consortium. Leukemia 2012;26:972-972.

Krishnan B, Else M, Tjonnfjord G, et al. Stem cell transplantation after alemtuzumab in T-cell prolymphocytic leukaemia results in longer survival than after alemtuzumab alone: a multicentre retrospective study. Br J Haematol 2010;149: 907–910.

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 3.2018
Extranodal NK/T-Cell Lymphoma, nasal type

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DIAGNOSIS[a]

ESSENTIAL:

- **Hematopathology review of all slides with at least one paraffiin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.**
- **Excisional or incisional biopsy is preferred over core needle biopsy. An FNA biopsy alone is not sufficient for the initial diagnosis of lymphoma.[b] A core needle biopsy is not optimal but can be used under certain circumstances. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core needle biopsy and FNA biopsy in conjunction with appropriate ancillary techniques may be sufficient for diagnosis.**
- **Adequate immunophenotyping to establish diagnosis[c,d]**
  - **IHC panel: For high clinical suspicion of NKTL, first panel should include: cCD3ε, CD56, EBER-ISH[e]**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **Molecular analysis to detect clonal T-cell antigen receptor (TCR) gene rearrangements[f] or other assessment of clonality[g]**
- **IHC panel:**
  - **B-cell lineage: CD20**
  - **T-cell lineage: CD2, CD7, CD8, CD4, CD5**
  - **Other: CD30, Ki-67**

SUBTYPES

Subtypes included:

- **Extranodal NK/T-cell, nasal type** → **See Workup (NKTL-2)**

Subtypes *not* included:

- **NK-cell leukemias**
- **Precursor NK-cell neoplasm**

[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+, cCD3ε+ (surface CD3-), CD4-, CD5-, CD7-/+, CD8-/+, CD43+, CD45RO+, CD56+, T-cell receptor (TCR)αß-, TCRγδ-, EBV-EBER+. TCR and Ig genes are germline (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+ TCRαß or γδ+, cytotoxic granule proteins +. TCR genes are clonally rearranged.

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

[f] TCR clonal gene rearrangement results should be interpreted with caution. TCR clonal gene rearrangement can be seen in non-malignant conditions or may not be demonstrated in all cases of CTCL. Demonstration of identical clones in skin, blood, and/or lymph node may be helpful in selected cases.

[g] Such as FISH, karyotype, genomic analysis.

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WORKUP

ESSENTIAL:

- **History and physical exam with attention to node-bearing areas (including Waldeyer's ring), testicles, and skin**
- **ENT evaluation of nasopharynx**
- **Performance status**
- **B symptoms**
- **CBC with differential**
- **LDH**
- **Comprehensive metabolic panel**
- **Uric acid**
- **Bone marrow biopsy + aspirate[h]**
- **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)[i]**
- **Echocardiogram or MUGA scan if treatment includes regimens containing anthracyclines or anthracenedione**
- **EBV viral load[j] by quantitative PCR**
- **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**

→ **See Induction Therapy (NKTL-3)**

[h]BM aspirate - lymphoid aggregates are rare, and are considered involved if EBER-1 positive; hemophagocytosis may be present.
[i]See Prognostic Index of Natural Killer Lymphoma (PINK) (NKTL-A).
[j]EBV viral load is important in diagnosis and possibly in monitoring of disease. A positive result is consistent with NK/T-cell, nasal type. Lack of normalization of EBV viremia should be considered indirect evidence of persistent disease.

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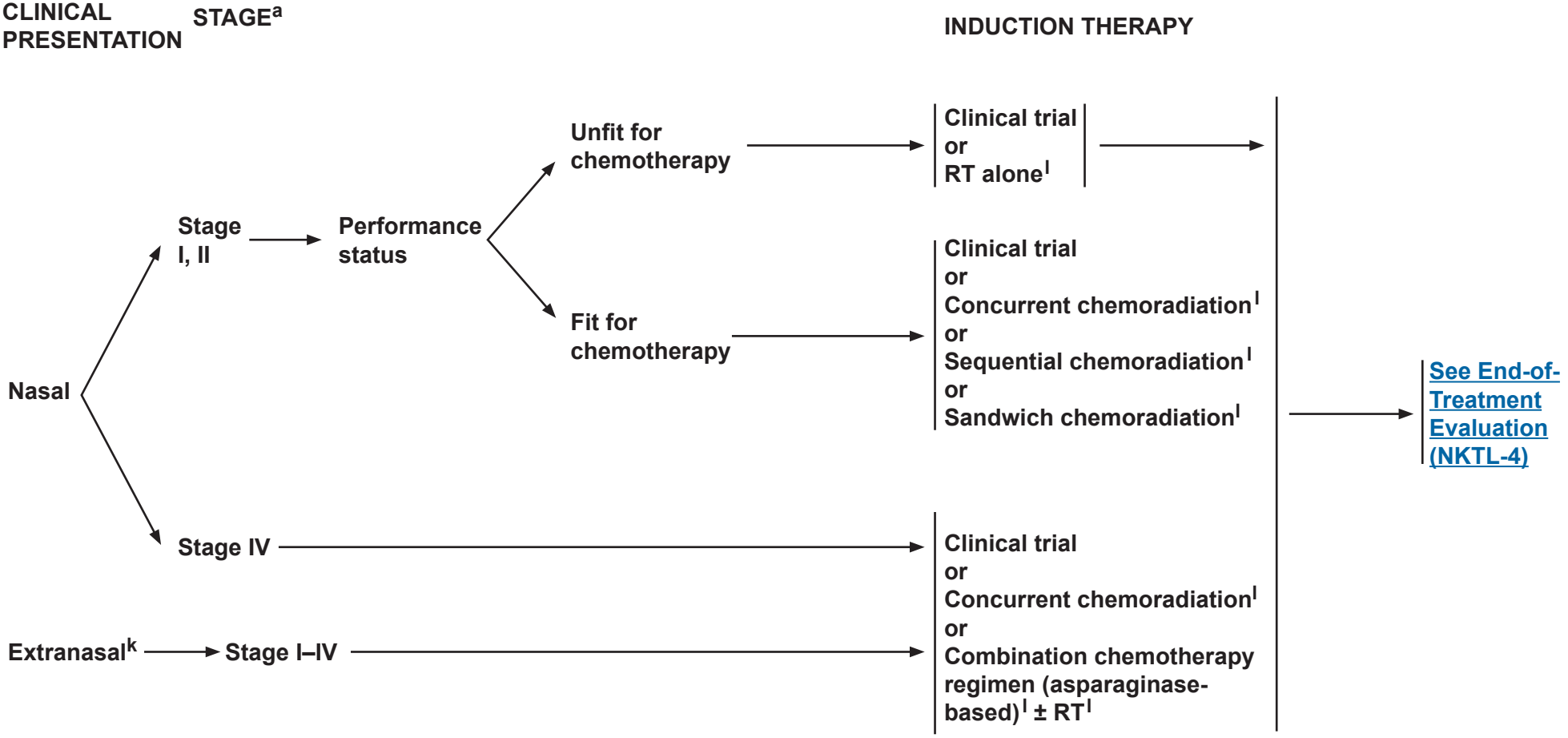

Consider prophylaxis for tumor lysis syndrome (See LYMPH-A)

[a]It is preferred that treatment occur at centers with expertise in the management of this disease.
[k]In rare circumstances of stage I_E primary cutaneous NK/T-cell lymphoma, IFRT for solitary skin lesions can be considered.
[l]See Suggested Treatment Regimens (NKTL-B).

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NCCN Guidelines Version 3.2018
Extranodal NK/T-Cell Lymphoma, nasal type

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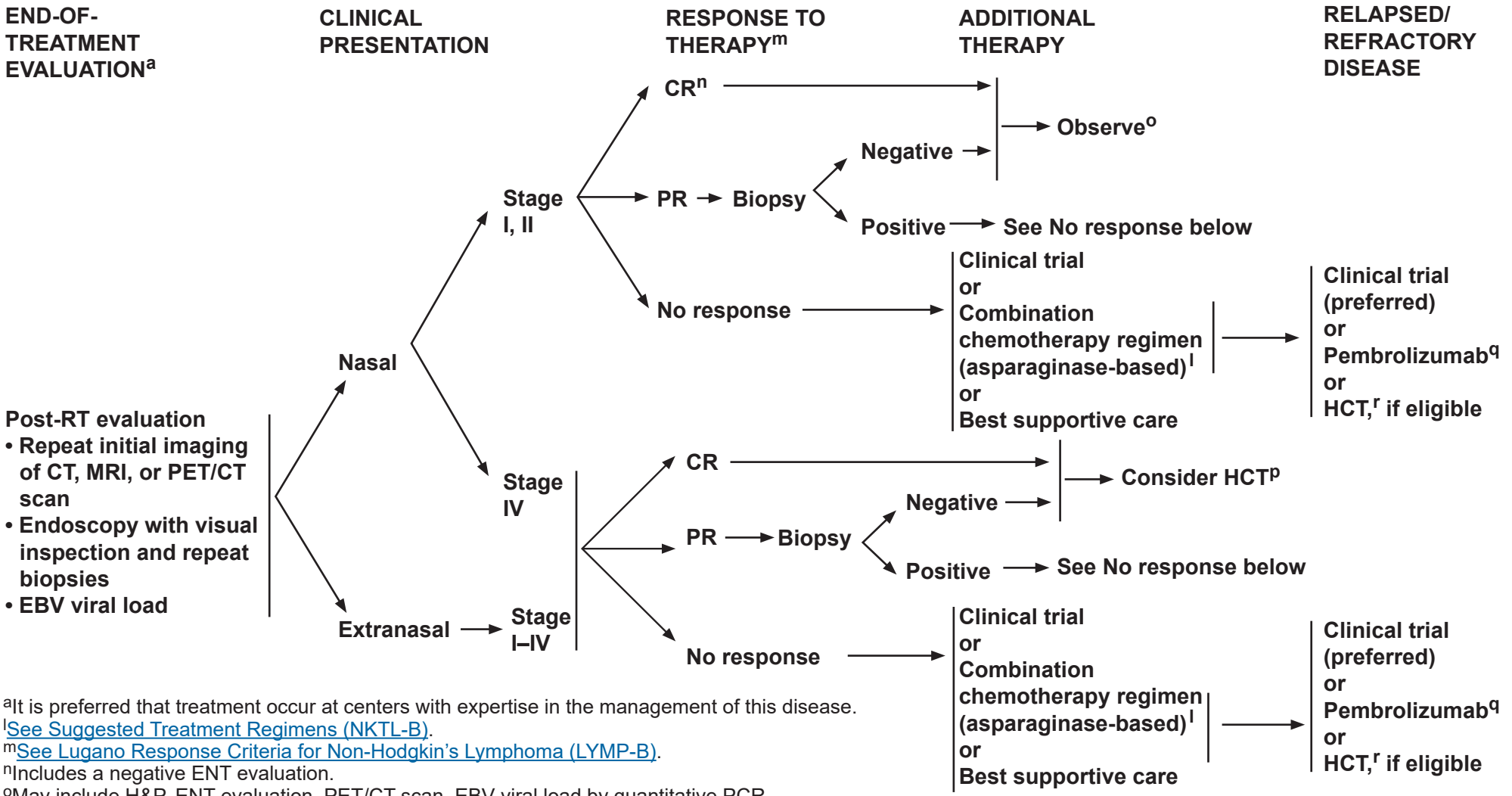

[a]It is preferred that treatment occur at centers with expertise in the management of this disease.
[l]See Suggested Treatment Regimens (NKTL-B).
[m]See Lugano Response Criteria for Non-Hodgkin's Lymphoma (LYMP-B).
[n]Includes a negative ENT evaluation.
[o]May include H&P, ENT evaluation, PET/CT scan, EBV viral load by quantitative PCR.
[p]There are no clear data to suggest whether allogeneic or autologous HSCT is preferred and treatment should be individualized.
[q]Clinical trial is the preferred relapsed/refractory option. In the absence of a clinical trial, pembrolizumab is an appropriate option.
[r]Allogeneic preferred, if donor available.

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PROGNOSTIC INDEX OF NATURAL KILLER CELL LYMPHOMA (PINK)[a]

RISK FACTORS

Age >60 y
Stage III or IV disease
Distant lymph-node involvement
Non-nasal type disease

	Number of risk factors
Low	0
Intermediate	1
High	≥2

PROGNOSTIC INDEX OF NATURAL KILLER CELL LYMPHOMA WITH EPSTEIN-BARR VIRUS DNA (PINK-E)[a]

RISK FACTORS

Age >60 y
Stage III or IV disease
Distant lymph-node involvement
Non-nasal type disease
Epstein-Barr virus DNA

	Number of risk factors
Low	0-1
Intermediate	2
High	≥3

[a]Kim SJ, Yoon DH, Jaccard A, et al. A prognostic index for natural killer cell lymphoma after non-anthracycline-based treatment: a multicentre, retrospective analysis. Lancet Oncol 2018;17:389-400.

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SUGGESTED TREATMENT REGIMENS[a]

(in alphabetical order)

Combination chemotherapy regimen (asparaginase-based)[b,c]
- AspaMetDex (pegaspargase, methotrexate, and dexamethasone)
- Modified-SMILE (steroid [dexamethasone], methotrexate, ifosfamide, pegaspargase, and etoposide) x 4–6 cycles for advanced stage
- P-GEMOX (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, modified-SMILE x 2–4 cycles followed by RT 45–50.4 Gy

Sandwich chemoradiation[c]
- P-GEMOX x 2 cycles followed by RT 56 Gy followed by P-GEMOX 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.

[a]See references for regimens NKTL-B 2 of 2.
[b]See Asparaginase Toxicity Management in the NCCN Guidelines for Acute Lymphoblastic Leukemia.
[c]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. P-GEMOX is an option for selected patients who cannot tolerate intense chemotherapy.

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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
References

Combination Chemotherapy Regimen

Yamaguchi M, Kwong YL, Kim WS, et al. Phase II study of SMILE chemotherapy for newly diagnosed stage IV, relapsed, or refractory extranodal natural killer (NK)/T-cell lymphoma, nasal type: The NK-Cell Tumor Study Group Study. J Clin Oncol 2011;29:4410-4416.

Lunning M, Pamer E, Maragulia J, et al. Modified SMILE (mSMILE) is Active in the Treatment of Extranodal Natural Killer/T-Cell Lymphoma: A Single Center US Experience. Clinical Lymphoma, Myeloma and Leukemia 2014;14:S143-S144.

Jaccard A, Gachard N, Marin B, et al. Efficacy of L-asparaginase with methotrexate and dexamethasone (AspaMetDex regimen) in patients with refractory or relapsing extranodal NK/T-cell lymphoma, a phase 2 study. Blood 2011;117:1834-1839.

Wang JH, Wang H, Wang YJ, et al. Analysis of the efficacy and safety of a combined gemcitabine, oxaliplatin and pegaspargase regimen for NK/T-cell lymphoma. Oncotarget 2018;7:35412-35422.

Qi S, Yahalom J, Hsu M, et al. Encouraging experience in the treatment of nasal type extra-nodal NK/T-cell lymphoma in a non-Asian population. Leuk Lymphoma 2018;57:2575-2583.

Concurrent Chemoradiation

Yamaguchi M, Tobinai K, Oguchi M, et al. Concurrent chemoradiotherapy for localized nasal natural killer/T-cell lymphoma: an updated analysis of the Japan clinical oncology group study JCOG0211. J Clin Oncol 2012;30:4044-4046.

Kim SJ, Kim K, Kim BS, et al. Phase II trial of concurrent radiation and weekly cisplatin followed by VIPD chemotherapy in newly diagnosed, stage IE to IIE, nasal, extranodal NK/T-cell lymphoma: Consortium for Improving Survival of Lymphoma study. J Clin Oncol 2009;27:6027-6032.

Yamaguchi M, Suzuki R, Oguchi M, et al. Treatments and Outcomes of Patients With Extranodal Natural Killer/T-Cell Lymphoma Diagnosed Between 2000 and 2013: A Cooperative Study in Japan. J Clin Oncol 2018;35:32-39.

Sequential Chemoradiation

Lunning M, Pamer E, Maragulia J, et al. Modified SMILE (mSMILE) is Active in the Treatment of Extranodal Natural Killer/T-Cell Lymphoma: A Single Center US Experience. Clinical Lymphoma, Myeloma and Leukemia 2014;14:S143-S144.

Sandwich Chemoradiation

Tse E, Kwong YL. The diagnosis and management of NK/T-cell lymphomas. J Hematol Oncol 2018;10:85.

Wang L, Wang ZH, Chen XQ, et al. First-line combination of GELOX followed by radiation therapy for patients with stage IE/IIE ENKTL: An updated analysis with long-term follow-up. Oncol Lett 2015;10:1036-1040.

Bi XW, Xia Y, Zhang WW, et al. Radiotherapy and PGEMOX/GELOX regimen improved prognosis in elderly patients with early-stage extranodal NK/T-cell lymphoma. Ann Hematol 2015;94:1525-1533.

Radiation Therapy Alone

Huang MJ, Jiang Y, Liu WP, et al. Early or up-front radiotherapy improved survival of localized extranodal NK/T-cell lymphoma, nasal-type in the upper aerodigestive tract. Int J Radiat Oncol Biol Phys 2008;70:166-174.

Relapsed/Refractory Therapy

Kwong YL, Chan TSY, Tan D, et al. PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing l-asparaginase. Blood 2018;129:2437-2442.

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SUPPORTIVE CARE

Tumor Lysis Syndrome (TLS)

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

- 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
      or
      Rasburicase is indicated for patients with any of the following risk factors:
      - presence of any high-risk feature
      - urgent need to initiate therapy in a high-bulk patient
      - situations where adequate hydration may be difficult or impossible
      - Acute renal failure
    - ◊ One dose of rasburicase is frequently adequate. 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.

Supportive Care
continued on next page

[a]There are data to support that fixed-dose rasburicase is very effective in adult patients.

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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.**
- **Herpes virus prophylaxis with acyclovir or equivalent**
- **PJP prophylaxis with sulfamethoxazole/trimethoprim or equivalent**
- **Consider antifungal prophylaxis**
- **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.

Response	Site	PET-CT (Metabolic response)	CT (Radiologic response)[d]
Complete response	Lymph nodes and extralymphatic sites	Score 1, 2, or 3[a] with or without a residual mass on 5 point scale (5-PS)[b,c]	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
	Non-measured lesion	Not applicable	Absent
	Organ enlargement	Not applicable	Regress to normal
	New Lesions	None	None
	Bone Marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, and flow cytometry IHC negative
Partial response	Lymph nodes and extralymphatic sites	Score 4 or 5[b] 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

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.

Response	Site	PET-CT (Metabolic response)	CT (Radiologic response) [d]
No response or stable disease	Target nodes/nodal masses, extranodal lesions	Score 4 or 5[b] with no significant change in FDG uptake from baseline at interim or end of treatment. No new or progressive lesions	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
	Non-measured lesion	Not applicable	No increase consistent with progression
	Organ enlargement	Not applicable	No increase consistent with progression
	New Lesions	None	None
	Bone Marrow	No change from baseline	Not applicable
Progressive disease	Individual target nodes/nodal masses Extranodal lesions	Score 4 or 5 [b] 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[e]	Requires at least one of the following PPD progression: An individual node/lesion must be abnormal with: LDi >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 >2 cm In the setting of splenomegaly, the splenic length must increase by >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
	Non-measured lesion	None	New or clear progression of preexisting nonmeasured lesions
	New Lesions	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[e]	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <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
	Bone Marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Footnotes on LYMP-B 3 of 3

Continued on next page

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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 quantitiatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses and other lesions that cannot be confirmed and followed by imaging.

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PRINCIPLES OF RADIATION THERAPY[a]

- **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.**

Continued on next page

[a]See references on LYMP-C 4 of 4.

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PRINCIPLES OF RADIATION THERAPY[a]

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.

Continued on next page

[a]See references on LYMP-C 4 of 4.

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PRINCIPLES OF RADIATION THERAPY[a]

General Dose Guidelines: (RT in conventional fraction sizes)

- **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 hematopoietic 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: 24–36 Gy**

[a]See references on LYMP-C 4 of 4.

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.

PRINCIPLES OF RADIATION THERAPY

REFERENCES

Filippi AR, Ragona R, Fusella M, et al. Changes in breast cancer risk associated with different volumes, doses, and techniques in female Hodgkin lymphoma patients treated with supra-diaphragmatic radiation therapy. Pract Radiat Oncol 2013;3:216-222.

Girinsky T, Pichenot C, Beaudre A, et al. Is intensity-modulated radiotherapy better than conventional radiation treatment and three-dimensional conformal radiotherapy for mediastinal masses in patients with Hodgkin's disease, and is there a role for beam orientation optimization and dose constraints assigned to virtual volumes? Int J Radiat Oncol Biol Phys 2006;64:218-226.

Horning SJ, Weller E, Kim K, et al. Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-Hodgkin's lymphoma: Eastern Cooperative Oncology Group study 1484. J Clin Oncol 2004;22:3032-3038.

Hoskin PJ, Díez P, Williams M, et al. Recommendations for the use of radiotherapy in nodal lymphoma. Clin Oncol (R Coll Radiol) 2013;25:49-58.

Illidge T, Specht L, Yahalom J, et al. Modern radiation therapy for nodal non-Hodgkin lymphoma-target definition and dose guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys 2014 1;89:49-58.

Li YX, Wang H, Jin J, et al. Radiotherapy alone with curative intent in patients with stage I extranodal nasal-type NK/T-cell lymphoma. Int J Radiat Oncol Biol Phys 2012;82:1809-1815.

Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med 1998;339:21-26.

Nieder C, Schill S, Kneschaurek P, Molls M. Influence of different treatment techniques on radiation dose to the LAD coronary artery. Radiat Oncol 2007;2:20.

Wang H, Li YX, Wang WH, et al. Mild toxicity and favorable prognosis of high-dose and extended involved-field intensity-modulated radiotherapy for patients with early-stage nasal NK/T-cell lymphoma. Int J Radiat Oncol Biol Phys 2012;82:1115-1121.

Yahalom J, Illidge T, Specht L, Hoppe RT, et al. Modern Radiation Therapy for Extranodal Lymphomas: Field and Dose Guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys 2015;92:11-31.

Million L, Yi EJ, Wu F, et al. Radiation therapy for primary cutaneous anaplastic large cell lymphoma: An International Lymphoma Radiation Oncology Group Multi-institutional Experience. Int J Radiat Oncol Biol Phys 2018;95:1454-1459.

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.

Classification

Table 1

WHO Classification of the Mature B-Cell, T-Cell, and NK-Cell Neoplasms (2018)

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
- Extranodal 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 B*CL2* 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

Table 1 continued

WHO Classification of the Mature B-Cell, T-Cell, and NK-Cell Neoplasms (2018)

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
- Extranodal NK/T-cell lymphoma, nasal type
- 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 anaplastic large cell lymphoma
- 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.

Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD, Jaffe ES. The 2018 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2018;127:2375-2390.

Staging

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

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

*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.

 Cheson B, Fisher R, Barrington S, et al. Recommendations for Initial Evaluation, Staging and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma – the Lugano Classification. J Clin Oncol 2014;32:3059-3067.

Discussion

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 indicated.

Table of Contents

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 2018, an estimated 74,680 people will be diagnosed with NHL and there will be approximately 19,910 deaths due to the disease.[1] NHL is the seventh leading site of new cancer cases among men and women in the United States, accounting for 4% to 5% of new cancer cases and 3% to 4% of cancer-related deaths.[1] Prospectively collected data from the National Cancer Data Base showed that 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 lymphoma (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 and 2011.[2]

The incidence of NHL has increased from 2001 to 2012, particularly for B-cell neoplasms.[3] 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.[4] As a result, patients with NHL may also have significant comorbid conditions, which complicate treatment options.

The National Comprehensive Cancer Network (NCCN®) Clinical Practice Guidelines in Oncology (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, supportive care, and surveillance strategies for the most common subtypes of NHL.

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

- Peripheral T-cell lymphomas (PTCL)
- Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL)
- Mycosis fungoides (MF) and Sézary syndrome (SS)
- Primary cutaneous CD30+ T-cell lymphoproliferative disorders
- T-cell large granular lymphocytic leukemia (TGLL)
- Adult T-cell leukemia/lymphoma (ATLL)
- T-cell prolymphocytic leukemia (TPLL)
- Extranodal NK/T-cell lymphomas (ENKL), nasal type

Response Assessment

The International Working Group (IWG) first published the guidelines for response criteria for lymphoma in 1999 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.[5] These response criteria were revised in 2007 by the International Harmonization Project to incorporate immunohistochemistry (IHC), flow cytometry, and 18-fluorodeoxyglucose (FDG)-PET scans in the definition of response for lymphoma.[6] 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), relapsed disease, or

progressive disease (PD). In 2014, revised response criteria, known as the Lugano response criteria, were introduced for staging and response assessment using PET/CT scans.[7,8] PET/CT is recommended for initial staging of all FDG-avid lymphomas. The use of a 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.[9-11] 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 to 2 or 1 to 3 to be PET negative, while scores of 4 to 5 are universally considered PE positive. A score of 4 on an interim or end-of-treatment restaging scan may be consistent with a PR if the FDG avidity has declined from initial staging, while a score of 5 denotes PD. 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.

Staging

PET/CT scans are now employed for initial staging, restaging, and end-of-treatment response assessment in the majority of patients with NHL. PET is positive at diagnosis in 90% of patients with T-cell lymphoma.[12] 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 in only 15% to 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.[13,14] 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.[13] 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.[14] 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.[8]

PET/CT is recommended for initial staging of FDG-avid lymphomas. PET should be done with contrast-enhanced diagnostic CT. 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 on 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. 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 (IGRT), respiratory gating, or deep inspiration breath hold.[15,16] 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.[15-18]

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 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 (eg, lungs, bone, muscle, 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.[15,16] ISRT targets the initially involved nodal and extranodal sites detectable at presentation.[15,16] Larger RT fields should be considered for limited-stage indolent NHL, often treated with RT alone.[15]

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.[15]

The principles of ISRT are similar for both nodal and extranodal disease. The gross tumor volume (GTV) defined by radiologic imaging prior to biopsy, chemotherapy, or surgery provides the basis for determining the clinical target volume (CTV).[19] 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, the whole organ (eg, stomach, salivary gland, thyroid) comprises the CTV in most cases. For other organs, including orbit, breast, lung, bone, and 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 treatment planning recommendations and general dose guidelines for individual subtypes of T-cell lymphomas are outlined in the “Principles of RT” section of the guidelines.

Supportive Care

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.[20] Untreated TLS can induce profound metabolic changes resulting in cardiac arrhythmias, seizures, loss of muscle control, acute renal failure, and even death.

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.[21] 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, hypocalcemia, and elevated creatinine. 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, rapidly proliferative or aggressive hematologic malignancies, spontaneous TLS, elevated while blood cell count, bone marrow involvement, pre-existing elevated uric acid, ineffectiveness of allopurinol and renal disease, or renal involvement by tumor.

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.[22] 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.[23] 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).[23] 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.[23] 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).[24] 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.[24]

A prospective, multicenter, randomized phase III trial compared the efficacy and safety of rasburicase and allopurinol in adult patients with hematologic malignancies at high or potential risk for TLS (N = 275).[25] 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.[25] 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.[25] 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.[25] 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)[26,27] or a single weight-based dose of rasburicase (0.05–0.15 mg/kg)[28,29] 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).[30] 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.[30] 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.[30]

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 the 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 treatment and at retreatment of hyperuricemia. Allopurinol should be started 2 to 3 days prior to chemotherapy and continued for 10 to 14 days. Rasburicase is recommended for patients with any of the following risk factors: presence of any high-risk feature (ie, 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; allopurinol is ineffective; or acute renal failure. A single dose is adequate in most cases; repeat dosing should be given on an individual basis.

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 preemptive 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. Herpes virus prophylaxis with acyclovir or equivalent and pneumocystis jirovecii pneumonia (PJP) prophylaxis with sulfamethoxazole/trimethoprim or equivalent is recommended for patients receiving alemtuzumab-based regimens. Antifungal prophylaxis should be considered.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a rare but serious and usually fatal central nervous system (CNS) infection caused by reactivation of the latent JC polyomavirus. Patients with NHL receiving treatment with the anti-CD30 antibody-drug conjugate brentuximab vedotin may be at potential risk for PML.[31] 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. Development of PML is clinically suspected based on neurologic signs and symptoms that may include confusion, motor weakness or poor motor coordination, visual changes, and/or speech changes.[31] 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 neurologic symptoms. There is currently no consensus on pretreatment evaluations that can be undertaken to predict for the subsequent development of PML.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7-30. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29313949.

2. Al-Hamadani M, Habermann TM, Cerhan JR, et al. Non-Hodgkin lymphoma subtype distribution, geodemographic patterns, and survival in the US: A longitudinal analysis of the National Cancer Data Base from 1998 to 2011. Am J Hematol 2015;90:790-795. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26096944.

3. Teras LR, DeSantis CE, Cerhan JR, et al. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. CA Cancer J Clin 2016;66:443-459. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27618563.

4. Groves FD, Linet MS, Travis LB, Devesa SS. Cancer surveillance series: non-Hodgkin's lymphoma incidence by histologic subtype in the United States from 1978 through 1995. J Natl Cancer Inst 2000;92:1240-1251. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10922409.

5. Cheson BD, Horning SJ, Coiffier B, et al. Report of an International Workshop to standardize response criteria for Non-Hodgkin's Lymphomas. J Clin Oncol 1999;17:1244-1253. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10561185.

6. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579-586. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17242396.

7. Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of Imaging in the Staging and Response Assessment of Lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25113771.

8. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32:3059-3068. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25113753.

9. Barrington SF, Qian W, Somer EJ, et al. Concordance between four European centres of PET reporting criteria designed for use in multicentre trials in Hodgkin lymphoma. Eur J Nucl Med Mol Imaging 2010;37:1824-1833. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20505930.

10. Meignan M, Gallamini A, Haioun C, Polliack A. Report on the Second International Workshop on interim positron emission tomography in lymphoma held in Menton, France, 8-9 April 2010. Leuk Lymphoma 2010;51:2171-2180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21077737.

11. Meignan M, Gallamini A, Itti E, et al. Report on the Third International Workshop on Interim Positron Emission Tomography in Lymphoma held in Menton, France, 26-27 September 2011 and Menton 2011 consensus. Leuk Lymphoma 2012;53:1876-1881. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22432519.

12. Feeney J, Horwitz S, Gonen M, Schoder H. Characterization of T-cell lymphomas by FDG PET/CT. AJR Am J Roentgenol 2010;195:333-340. Available at: http://www.ncbi.nlm.nih.gov/entrez/20651187.

13. Schaefer NG, Hany TF, Taverna C, et al. Non-Hodgkin lymphoma and Hodgkin disease: coregistered FDG PET and CT at staging and restaging--do we need contrast-enhanced CT? Radiology 2004;232:823-829. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15273335.

14. Rodriguez-Vigil B, Gomez-Leon N, Pinilla I, et al. PET/CT in lymphoma: prospective study of enhanced full-dose PET/CT versus

unenhanced low-dose PET/CT. J Nucl Med 2006;47:1643-1648. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17015900.

15. Illidge T, Specht L, Yahalom J, et al. Modern radiation therapy for nodal non-Hodgkin lymphoma-target definition and dose guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys 2014;89:49-58. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24725689.

16. Yahalom J, Illidge T, Specht L, et al. Modern radiation therapy for extranodal lymphomas: field and dose guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys 2015;92:11-31. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25863750.

17. Nieder C, Schill S, Kneschaurek P, Molls M. Influence of different treatment techniques on radiation dose to the LAD coronary artery. Radiat Oncol 2007;2:20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17547777.

18. Charpentier AM, Conrad T, Sykes J, et al. Active breathing control for patients receiving mediastinal radiation therapy for lymphoma: Impact on normal tissue dose. Pract Radiat Oncol 2014;4:174-180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24766684.

19. Hoskin PJ, Diez P, Williams M, et al. Recommendations for the use of radiotherapy in nodal lymphoma. Clin Oncol (R Coll Radiol) 2013;25:49-58. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22889569.

20. Coiffier B, Altman A, Pui C, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol 2008;26:2767-2778. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18509186.

21. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol 2004;127:3-11. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15384972.

22. Krakoff IH, Meyer RL. Prevention of hyperuricemia in leukemia and lymphoma: use of alopurinol, a xanthine oxidase inhibitor. . JAMA 1965;193:1-6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14297704.

23. Bosly A, Sonet A, Pinkerton CR, et al. Rasburicase (recombinant urate oxidase) for the management of hyperuricemia in patients with cancer: report of an international compassionate use study. Cancer 2003;98:1048-1054. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12942574.

24. Coiffier B, Mounier N, Bologna S, et al. Efficacy and safety of rasburicase (recombinant urate oxidase) for the prevention and treatment of hyperuricemia during induction chemotherapy of aggressive non-Hodgkin's lymphoma: results of the GRAAL1 (Groupe d'Etude des Lymphomes de l'Adulte Trial on Rasburicase Activity in Adult Lymphoma) study. J Clin Oncol 2003;21:4402-4406. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14581437.

25. Cortes J, Moore JO, Maziarz RT, et al. Control of plasma uric acid in adults at risk for tumor lysis syndrome: efficacy and safety of rasburicase alone and rasburicase followed by allopurinol compared with allopurinol alone-results of a multicenter phase III study. J Clin Oncol 2010;28:4207-4213. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20713865.

26. McDonnell AM, Lenz KL, Frei-Lahr DA, et al. Single-dose rasburicase 6 mg in the management of tumor lysis syndrome in adults. Pharmacotherapy 2006;26:806-812. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16716134.

27. Vines AN, Shanholtz CB, Thompson JL. Fixed-dose rasburicase 6 mg for hyperuricemia and tumor lysis syndrome in high-risk cancer patients. Ann Pharmacother 2010;44:1529-1537. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20841516.

28. Campara M, Shord SS, Haaf CM. Single-dose rasburicase for tumour lysis syndrome in adults: weight-based approach. J Clin Pharm

Ther 2009;34:207-213. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19250141.

29. Knoebel RW, Lo M, Crank CW. Evaluation of a low, weight-based dose of rasburicase in adult patients for the treatment or prophylaxis of tumor lysis syndrome. J Oncol Pharm Pract 2011;17:147-154. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20332174.

30. Vadhan-Raj S, Fayad LE, Fanale MA, et al. A randomized trial of a single-dose rasburicase versus five-daily doses in patients at risk for tumor lysis syndrome. Ann Oncol 2012;23:1640-1645. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22015451.

31. Carson KR, Newsome SD, Kim EJ, et al. Progressive multifocal leukoencephalopathy associated with brentuximab vedotin therapy: a report of 5 cases from the Southern Network on Adverse Reactions (SONAR) project. Cancer 2014;120:2464-2471. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24771533.

Mycosis Fungoides and Sézary Syndrome

Overview

Cutaneous T-cell lymphomas (CTCLs) are a group of NHLs of mature T cells that primarily present in the skin, and at times progress to involve lymph nodes, blood, and visceral organs. MF is the most common subtype with primary cutaneous involvement and SS is an erythrodermic, leukemic variant of CTCL that is characterized by significant blood involvement and lymphadenopathy.[1] MF accounts for about 50% to 70% of CTCLs while SS accounts for only 1% to 3% of CTCLs.[2,3] In a population-based study of 3884 patients with cutaneous lymphomas diagnosed during 2001 to 2005, MF and SS were diagnosed in 1487 patients (38%) and 33 patients (less than 1%; 0.8%), respectively.[3] In 2016, an estimated 1620 people were diagnosed with MF and 70 people were diagnosed with SS in the United States.[4]

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for T-Cell Lymphomas, an electronic search of the PubMed database was performed to obtain key literature in MF and SS published between May 2016 and November 2017 using the following search terms: cutaneous T-cell lymphomas, mycosis fungoides, and Sezary syndrome. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[5]

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 193 citations and their potential relevance was examined. The data from key PubMed articles selected by the panel for review during the Guidelines update meeting as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). 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 website.

Staging

The TNM staging system was first developed by the Mycosis Fungoides Cooperative Group (MFCG) and has since been revised by the EORTC and the International Society for Cutaneous Lymphomas (ISCL) based on new data that emerged in the area of immunohistochemistry, biology, and prognosis of MF and SS.[6,7]

In the revised staging system, T1 disease is defined as less than 10% of the skin surface involvement with patches, papules, and/or plaques and T4 disease is defined as erythroderma with at least 80% of the skin surface diffusely involved. However, this criterion of 80% is subjective and the surface area can fluctuate in patients with erythrodermic CTCL. Thus, other features including keratoderma, ectropion, or leg edema should also be evaluated in patients with erythrodermic CTCL. 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.[6,7]

Lymph node biopsy for staging is recommended only for clinically abnormal nodes (>1.5 cm in diameter). Patients can have lymphadenopathy that is clinically reactive or dermatopathic; thus, not all enlarged lymph nodes are sampled. The designation “Nx” may be used for abnormal lymph nodes without histologic evaluation. Visceral disease with the involvement of an organ (eg, 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 evaluation.

Blood involvement is classified into three groups: B0 is associated with the absence of significant blood involvement (≤5% of peripheral blood lymphocytes are atypical [Sézary] cells or <15% of total lymphocytes are CD4+/CD26- or CD4+/CD7- or otherwise aberrant in phenotype); B1 is defined as having a low tumor burden (>5% of peripheral blood lymphocytes are atypical [Sézary] cells or >15% of total lymphocytes are CD4+/CD26- or CD4+/CD7- or otherwise aberrant but do not meet the criteria for B2); and B2 is associated with high tumor burden with more than 1000 Sézary cells/mcL or increase in CD4+ cells with an abnormal phenotype (≥40% of total lymphocytes are CD4+/CD7- or ≥30% of total lymphocytes are CD+/CD26-).[6,7] According to the revised criteria, stage III disease is further divided into two subgroups, stages IIIA and IIIB, based on the extent of blood involvement (B0 and B1, respectively). SS is defined by B2 blood involvement and the presence of clonal T-cell antigen receptor (*TCR*) gene rearrangements in the blood (clonally related to neoplastic T cells in the skin).[6,7]

Prognosis

Age at presentation, overall stage, extent and type of skin involvement (T classification), presence of extracutaneous disease, the extent of peripheral blood involvement (as defined by flow cytometric measurements of Sézary cell counts), elevated LDH, and the presence of large cell transformation (LCT) and folliculotropism have been identified as the most significant prognostic factors for survival in patients with MF.[8-16] In a retrospective cohort study of 525 patients with MF and SS, patient age, T classification, and presence of extracutaneous disease retained independent prognostic value in a multivariate analysis.[11] The risk of disease progression, development of extracutaneous disease, or death due to MF correlated with initial T classification. Limited patch or plaque disease has an excellent prognosis compared to tumor stage disease or erythrodermic skin involvement and extracutaneous disease is associated with a poor prognosis.[13,14]

LCT has been documented in a subgroup of patients with MF and 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 IIB disease and 56%–67% for stage IV disease).[17] LCT is often, but not always, aggressive. Age >60 years, advanced stage, high levels of LDH, and CD30 expression <10% were identified as risk factors for disease progression.[18,19] LCT is diagnosed when large cells are present in more than 25% of lymphoid/tumor cell infiltrates in a skin lesion biopsy.[20,21] CD30 expression is associated with LCT in MF or SS in 30% to 50% of cases and this finding may have potential implications for CD30-directed therapies.[17,21,22] Expert hematopathology review is needed to confirm the diagnosis, as LCT may not be easily distinguishable from other lymphoproliferative disorders.

Folliculotropic MF (FMF) may be an adverse prognostic variant of MF characterized by the infiltration of hair follicles by atypical T lymphocytes.[23-26] FMF typically presents as plaques and tumors mainly on the head/neck that are less responsive to skin-directed therapies and are also associated with higher risk of disease progression. Recent

studies have reported that FMF presents with two distinct patterns of clinicopathologic features with different prognostic implications (early stage and advanced stage).[27,28] The 5-year and 10-year OS rates were 92% and 72%, respectively, for early skin-limited FMF and the corresponding survival rates were 55% and 28%, respectively, for advanced skin-limited FMF.[28] Also, the risk profile for folliculotropism varies with stage of the disease. In early-stage MF (IA-IIA), folliculotropism is associated with either risk of disease progression or worse survival outcome, but in advanced-stage MF (IIB-IV) or SS, this feature is not an independent prognostic factor.[16]

In the Cutaneous Lymphoma International Consortium (CLIC) study that evaluated the relevance of prognostic markers on overall survival (OS) in 1275 patients with advanced-stage MF and SS, stage IV disease, age 60 years, LCT, and LDH levels were identified as independent prognostic markers that could be used together in a prognostic model to identify 3 risk groups with significantly different survival outcomes.[16] The 5-year survival rates were 68%, 44%, and 28%, respectively, for low-risk, intermediate-risk, and high-risk groups. A prospective international study by CLIC is underway to identify any new prognostic markers and validate the refined prognostic index model to optimize risk-stratified management in patients with MF and SS.

Diagnosis

Biopsy of suspicious skin sites and immunohistochemical studies of skin biopsy are essential to confirm the diagnosis. Bone marrow biopsy is not required for disease staging, but may be helpful in those with an unexplained hematologic abnormality.[6,7] Fine-needle aspiration (FNA) sampling is often inadequate. Excisional (preferred) or core needle biopsy of suspicious lymph nodes (ie, palpable nodes >1.5 cm in diameter and/or firm, irregular, clustered, or fixed nodes) and/or assessment of peripheral blood for Sézary cells are recommended in the absence of a definitive skin diagnosis.

MF and SS cells are typically characterized by the following immunophenotype: CD2+, CD3+, CD5+, CD4+, CD8-, CCR4+, TCR-beta+, and CD45RO+ and they lack certain T-cell markers, CD7 and CD26.[29] However, there are subtypes of MF that are CD8+ (especially the hypopigmented variant) or CD4/CD8 dual negative (in those with LCT), although rare. 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. The immunohistochemical panel may include CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, CD25, CD56, TIA1, granzyme B, and ßF1 (TCR-beta).

Molecular analysis to detect clonal *TCR* gene rearrangements 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 site.[30] A recent study evaluated the sensitivity and specificity of PCR-based TCR gamma and TCR beta clonality tests in distinguishing MF from inflammatory dermatoses, and reported that the combined use of these tests (in sequence) was more useful than a TCR gamma test alone. The researchers proposed an algorithm for the sequential use of these tests in patients with intermediate pretest probabilities of having MF.[31] However, results of the clonal TCR gene rearrangement analysis 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 nodes may be helpful in selected cases.

Assessment of peripheral blood for Sézary cells, including Sézary cell prep and flow cytometry to assess for expanded CD4+ cells with

increased CD4/CD8 ratio or with abnormal immunophenotype (including loss of CD7 or CD26), would be useful in cases where skin biopsy is not diagnostic and/or strongly suspicious of advanced-stage disease. Assessment of HTLV-1 status, either by HTLV-1 serology or other methods, may be useful in at-risk populations.

Workup

The initial workup of patients diagnosed with MF or SS involves a complete skin examination to assess the extent of the disease (ie, percent of BSA), type of skin lesion (eg, patch/plaque, tumor, erythroderma), and lymph nodes or other masses for the evaluation of lymphadenopathy or organomegaly.[6] Laboratory studies should include a complete blood count (CBC) with Sézary screen (manual slide review to identify Sézary cells) and Sézary flow cytometric study (optional for T1 disease). A comprehensive metabolic panel and assessment of LDH levels should also be part of the initial laboratory studies. Analysis of clonal *TCR* gene arrangement of peripheral blood lymphocytes is recommended if blood involvement is suspected. CT with contrast of the chest, abdomen, and pelvis or integrated whole body PET/CT scan is recommended for patients with unfavorable features (T2b or higher, FMF or LCT, palpable adenopathy, or abnormal laboratory studies) and should be considered for patients with T2a (patch disease with 10% or more BSA). 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.[32] Pregnancy testing should be done in women of child-bearing age if contemplating treatments that are contraindicated during pregnancy.

Treatment Options

Skin-Directed Therapies

Topical therapy with corticosteroids, mechlorethamine hydrochloride (nitrogen mustard), topical retinoids (eg, bexarotene) or topical imiquimod, or RT are indicated for patients with localized disease. Phototherapy [UVB or PUVA (psoralen and UVA)] and total skin electron beam therapy (TSEBT) are indicated for patients with widespread skin involvement (see *Skin-Directed Therapies* in the algorithm on MFSS-A).

Topical corticosteroids are effective, especially for the treatment of patch-stage MF, producing response rates of over 90%.[33] However, long-term use of a topical steroid may lead to skin atrophy or striae formation and the risk becomes greater with increased potency of the steroid. Moreover, high-potency steroids used on large skin surfaces may lead to systemic absorption.

Topical nitrogen mustard 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 nitrogen mustard.[34] The overall response rate (ORR) was 83% (CR in 50%). The 5-year relapse-free survival (RFS) rate for patients with a CR was 42%. The median OS for the entire cohort was 16 years and the actuarial 10-year OS rate was 71%.[34] Patients with T1 disease had a higher ORR (93% vs. 72%), CR rate (65% vs. 34%), longer median OS (21 months vs. 15 months), and higher 5-year OS rate (97% vs. 72%) than those with T2 disease.[34] The efficacy with topical nitrogen mustard was similar for aqueous and ointment preparations, although the ointment was associated with reduced hypersensitivity reactions. A multicenter randomized phase II trial evaluated the efficacy of a topical gel formulation of the nitrogen

mustard and the compounded ointment formulation in 260 patients with stage IA or IIA MF who had not been treated with topical nitrogen mustard within 2 years of study enrollment and had not received prior therapy with topical nitrogen mustard.[35] Response rate based on Composite Assessment of Index Lesion Severity was 59% 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.[35] These positive results led to the FDA approval of the topical gel formulation in 2013.

Bexarotene gel, the only FDA-approved synthetic retinoid for topical therapy in patients with MF and SS, was evaluated in two open-label, historically controlled clinical studies involving 117 patients with CTCL.[36,37] In the phase I-II trial involving 67 patients with early-stage MF, the ORR was 63% (CR in 21%) and the estimated median response duration was 99 weeks.[36] 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%).[37] 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.[38] Imiquimod has also demonstrated activity in a small number of patients with early-stage MF refractory to other therapies.[39-42] Given the common skin irritation toxicity observed with topical retinoids and imiquimod, these agents are best for treatment of localized, limited areas.

Radiation Therapy

MF is extremely radiosensitive and patients with stage IA MF may be managed effectively with local RT without adjuvant therapy.[43-45] In patients with unilesional MF (n = 18), treatment with local RT (most patients received an RT dose of 30.6 Gy) resulted in an ORR of 100%, with a 10-year RFS and OS rates of 86% and 100%, respectively.[43] Local superficial RT (median surface dose was 20 Gy) was associated with high disease-free survival (DFS) rates (75% at 5 years; 64% at 10 years) in patients with stage IA MF.[44] The 10-year DFS rate was 85% for patients with unilesional disease and the DFS rate was 91% for patients treated with ≥20 Gy. Low-dose IFRT has also been reported to induce high response rates without any toxicity in patients with MF.[46-48] In a study that included 31 patients with MF, low-dose RT (4 Gy in 2 fractions) resulted in a CR rate of only 30% whereas increasing the dose to 8 Gy in two fractions yielded a CR rate of 92%.[46] Patients in whom low-dose RT failed were retreated with 20 Gy in 8 fractions. In a large series of 58 patients treated with 8 Gy in a single fraction, the CR rate was 94% for individual lesions, after a median follow-up of 41 months.[47]

TSEBT has been shown to be effective in patients with early-stage MF, either alone or in combination with adjuvant therapy.[49,50] In a retrospective analysis involving 148 patients with T2 and T3 disease, TSEBT alone or in combination with adjuvant topical nitrogen mustard yielded significantly higher CR rates compared with nitrogen mustard alone (76% vs. 39% for T2; 44% vs. 8% for T3).[49] In another study involving patients with T1 or T2 disease (n = 57), TSEBT alone (mean total RT dose of 30 Gy) resulted in an ORR of 95% (CR 88% for patients with T1 disease and 85% for patients with T2 disease).[50] 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%.

Recent studies suggest that lower-dose TSEBT may be sufficiently active.[51,52] In a retrospective study of patients with T2 to T4 disease (n = 102, excluding those with extracutaneous disease), TSEBT doses of 5

Gy to <30 Gy resulted in an ORR (>50% improvement) of 96% and CR rate of 31%.[51] The ORR among the subgroup that received 5 Gy to <10 Gy (n = 19), 10 Gy to <20 Gy (n = 52), and 20 Gy to <30 Gy (n = 32) were 90%, 98%, and 97%, respectively. In patients with T2 or T3 disease, the CR rate with TSEBT 5 Gy to <30 Gy was higher among patients with T2 compared with T3 disease (41% vs. 17%). However, the OS and PFS outcomes were not significantly different by dose groups and were comparable to that of standard-dose TSEBT (≥30 Gy).[51] The efficacy of low-dose TSEBT (10–12 Gy over a period of 2–3 weeks) for stage IB-IV MF has also been confirmed in recent studies.[52-55] A pooled analysis of 3 phase II clinical trials that evaluated low-dose TSEBT (12 Gy; 1 Gy per fraction over 3 weeks) in 33 patients with MF reported an ORR of 88% (including 9 patients with a CR).[53] The median time to response and median duration of clinical benefit were 8 weeks and 71 weeks. The advantage of lower total dose includes fewer short-term complications and better ability to re-treat for PD. Further studies are warranted to confirm the use of low-dose TSEBT in combined modality regimens.

Phototherapy

Phototherapy with UVB (including narrowband) and photochemotherapy with PUVA are effective alternative treatment options for patients with early-stage MF.[56-60] In a retrospective analysis of patients with stage IA or IB, 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).[57] In another retrospective analysis of 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.[56] 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.[56] 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).[59] 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 patients with early patch-stage or thin-plaque disease.

Systemic Therapies

There are extensive data on many systemic therapeutic options for MF/SS, primarily from small clinical studies. Historically, the response criteria for MF/SS 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.

Conventional systemic chemotherapy has only modest activity in MF/SS and is used as a primary treatment only for patients with stages IIB-IV or LCT and as second-line therapy for stages IA-IIA refractory to skin-directed therapies and systemic biologic therapies.[61] Extracorporeal photopheresis (ECP), interferons (IFNs), systemic retinoids (bexarotene, all-trans retinoic acid [ATRA], isotretinoin [13-cis retinoic acid], and acitretin), histone deacetylase (HDAC) inhibitors (vorinostat or romidepsin), low-dose methotrexate (≤ 100 mg once a week), or brentuximab vedotin are preferred over conventional chemotherapy regimens for patients who do not respond to initial skin-directed therapies (see *SYST-CAT A* in the algorithm on MFSS-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.

ECP is an immunomodulatory therapy in which patient's leukocytes are removed by leukapheresis, treated extracorporeally with 8-methoxypsoralen and UVA, and then returned to the patient. ECP is generally given for at least 6 months 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, ECP has resulted in ORR ranging from about 50% to 70% (15%–30% CR). The median OS was 6 to 8 years, and the 5-year OS rate was reported to be 80% in one study.[62-66] Long-term follow-up data also confirmed the durability of responses in patients with MF/SS treated with ECP (31 patients with T4 disease and 8 patients with T2 disease).[66] After a median follow-up of 7 months, ECP resulted in a skin ORR of 74% (33% of patients achieved ≥50% partial skin response) and 41% of patients achieved ≥90% improvement after a median of 19.6 months. In a meta-analysis involving more than 400 patients with MF/SS, ECP as monotherapy resulted in 55.5% ORR with 15% CR.[67] The corresponding response rates were 58% (15% CR) for erythrodermic disease (T4) and 43% (9.5% CR) for SS.

IFN alpha as a single agent has produced ORR greater than 70% with CR rates greater than 20%.[68] IFN gamma has been shown to be effective in the treatment of patients with various stages of MF/SS that is refractory to IFN alpha and other topical or systemic therapies.[69]

Oral bexarotene has been evaluated for the treatment of refractory or persistent early- and advanced-stage MF/SS in two multicenter clinical trials.[70,71] In patients with stages IA-IIA MF/SS refractory to prior treatment, bexarotene (300 mg/m^2/day) was well tolerated and induced an ORR of 54%.[71] The rate of disease progression was 21%, and the median duration of response had not been reached at the time of the report. In patients with stages IIB–IVB MF/SS refractory to prior treatments, bexarotene (300 mg/m^2/day) induced clinical CR and PR in 45% of patients. At doses greater than 300 mg/m^2/day, the ORR was 55%, including a 13% clinical CR.[70] 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.[72] Bexarotene (oral capsules) is approved by the FDA for the treatment of refractory MF/SS.

Vorinostat was the first HDAC inhibitor to receive FDA approval for the treatment of patients with progressive, persistent, or recurrent MF/SS, on or following two systemic therapies. 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 (TTP) of 5 months.[73] Median TTP was greater than 9.8 months in responders with advanced disease (stage IIB or higher).[73] The response rates and median response durations appeared to be comparable to those obtained with bexarotene capsules. 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.[74]

Romidepsin, another HDAC inhibitor, also has demonstrated significant activity in MF/SS and is approved by the FDA for the treatment of patients with MF/SS who have received at least one prior systemic therapy.[75-77] In the pivotal phase IIB study (GPI-04-0001; 96 patients

with stage IB to IVA MF/SS; 71% had advanced-stage disease ≥ stage IIB; median 2 prior systemic therapies), romidepsin resulted in an ORR of 34% (CR in 6%). Among patients with advanced stages of disease, 38% achieved an objective response (CR in 7%).[76] 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.[76] An updated subanalysis from this pivotal trial confirmed that romidepsin has clinical activity across all disease compartments (skin, lymph nodes, and blood; no patient with visceral involvement was enrolled in the trial).[77] The compartment-specific ORRs were 40%, 35%, 32%, and 27%, respectively, for skin involvement, erythroderma, blood involvement, and lymphadenopathy.

Alemtuzumab, a humanized anti-CD52 monoclonal antibody, has shown promising activity in patients with advanced MF and SS.[78-83] In studies using standard-dose alemtuzumab (IV or subcutaneous [SC]; 30 mg 3 times a week 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.[78,79,82] The ORR was higher in patients with SS than those with advanced MF. In one multicenter retrospective analysis of 39 patients with SS (n = 23) or advanced MF (n =16), alemtuzumab resulted in an ORR of 51% for the whole study group (70% in patients with SS and 25% in patients with MF [*P* = .009]) and the median TTP was 3 months.[83] Major toxicities with alemtuzumab included myelotoxicities and infectious complications (including those attributed to CMV reactivation), thus prompting the investigation of lower doses of alemtuzumab.[80] 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.[80] 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.

Low-dose methotrexate has been used to treat early-stage MF and SS for many years, although only limited data are available.[84,85] Gemcitabine as a single agent has been evaluated in patients with advanced, heavily pretreated MF/SS and as front-line therapy in untreated patients.[86-88] Nucleoside analog pentostatin has shown activity either as a single agent or in combination with IFN alpha in patients with advanced MF or SS.[89,90] Limited data also suggest some activity for the oral alkylating agent temozolomide and the proteasome inhibitor bortezomib in patients with previously treated MF.[91,92]

Pralatrexate is a folate analog with demonstrated activity in patients with MF/SS.[93-95] In a multicenter dose-finding study, pralatrexate 10 mg/m^2 to 30 mg/m^2 (given weekly for 2 of 3 weeks or 3 of 4 weeks) was evaluated in patients with relapsed or refractory MF/SS (n = 54; MF, n = 38 [70%]; SS, n = 15 [28%]).[93] Patients had received a median of 4 prior systemic therapies (range, 1–11). The recommended dose was identified as 15 mg/m^2 weekly for 3 weeks of a 4-week cycle. The ORR for all evaluable patients in 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%).[93] Thus, low-dose pralatrexate was shown to have high activity in patients with heavily pretreated MF/SS. In the subgroup of patients with relapsed/refractory transformed MF (n = 12) treated on the PROPEL trial that evaluated pralatrexate (30 mg/m^2 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.[94] Based on investigator assessment, the median duration of response, median PFS, and OS were 4 months, 5 months, and 13 months, respectively.

Pegylated liposomal doxorubicin has shown substantial single-agent activity in patients with pretreated, advanced, or refractory MF/SS.[96-99] In a small prospective phase II trial in patients with previously treated MF/SS (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.[96] After a median follow-up of 23 months, the median EFS and OS were 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.[97] 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) that was refractory or relapsed after at least 2 prior systemic therapies (n = 49).[98] The ORR was 41% (CR in 6%). The median TTP 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%).[98] A recent phase II study evaluated pegylated liposomal doxorubicin followed sequentially by oral bexarotene in patients with advanced-stage or refractory MF/SS (n = 37; stage IV, n = 22 [including SS, n = 7]; stage IIB, n = 10; refractory, n = 6).[99] Treatment with 8 doses (16 weeks) of liposomal doxorubicin resulted in an ORR of 41% including clinical CR in 2 patients (n = 34 evaluable) with a median PFS of 5 months. The maximum response was observed after 16 weeks of treatment with liposomal doxorubicin; sequential bexarotene did not improve the response rate or duration.

Brentuximab vedotin, a CD30-targeting antibody-drug conjugate has been evaluated in patients with refractory or advanced MF and SS.[100,101] In a phase II study of 32 patients with refractory or advanced MF and SS (negligible to 100% CD30 expression levels), brentuximab vedotin resulted in an ORR of 70% (21 of 30 evaluable patients achieved an objective global response).[101] Although clinical responses with brentuximab vedotin were observed across all CD30 expression levels (including negligible CD30 expression), those with <5% CD30 expression had a lower likelihood of global response than those with ≥5% CD30 expression ($P < .005$). The safety and efficacy of brentuximab vedotin were further confirmed in a phase III randomized study.[102] In this study, 131 patients with previously treated CD30-expressing MF/SS (≥10% CD30-positive malignant cells or lymphoid infiltrate; 97 patients with MF/SS) were randomized to receive either brentuximab vedotin or physician's choice (methotrexate or bexarotene). At a median follow-up of 23 months, the primary endpoint, ORR lasting for ≥4 months was significantly higher for brentuximab vedotin compared to the physician's choice of treatment (56% vs. 13%; $P < .0001$) in the intent-to treat population. The proportion of patients achieving CR was also higher with brentuximab vedotin than with physician's choice (16% vs. 2%). Peripheral neuropathy was the most common adverse event reported in 67% of patients treated with brentuximab vedotin compared to 6% of patients in the physician's choice group.

Pembrolizumab, an immune checkpoint inhibitor, also has significant clinical activity in patients with previously treated MF/SS.[103] In a phase II study of 24 patients with MF/SS (stage IIB-IV) treated with at least one

prior systemic therapy, at a median follow-up of 40 weeks, pembrolizumab resulted in an ORR of 38%. The median PFS has not yet been reached and the one-year PFS rate was 69%. Skin flare reaction occurred exclusively in patients with SS and it should be distinguished from disease progression.

Combination Therapies

Combinations of biologic or non-cytotoxic therapies are used when single-agent therapies fail or for advanced, progressive, or refractory disease (see *Combination Therapies* in the algorithm on MFSS-A). The rationale for such systemic combination strategies is to provide synergistic efficacy without additive toxicities. Combinations of systemic and skin-directed therapies are often used to maximize clinical responses in the skin compartment. Most commonly used combination regimens include phototherapy plus either IFN or systemic retinoid,[104-111] and ECP plus either IFN or systemic retinoid or both.[63,112,113]

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.[104] In a prospective randomized study that 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%).[106] In a phase II trial in patients with symptomatic MF/SS (n = 63; stages IA-IIA, 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.[107] 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-IIA; n = 89), the combination of low-dose IFN alfa with PUVA resulted in an ORR of 98% (CR in 84%).[109] However, a phase III randomized study from the EORTC 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).[110] 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.[110] This trial was closed prematurely due to low patient accrual. A small prospective study evaluated the combination of low-dose bexarotene in combination with PUVA maintenance in 21 patients with MF/SS (stages IB-IV) resistant or intolerant to previous therapies.[111] The ORR was 85.6% after induction therapy with bexarotene (93.4% for early-stage disease and 66.6% for advanced disease). At the end of maintenance, the ORR was 76.2% (33.3% CR) and the median EFS for the whole group was 31 months.

The combination of IFN or systemic retinoids with ECP has been shown to improve response rates in patients with advanced-stage CTCL.[63,112,113] In a retrospective study involving patients with advanced CTCL (n = 47), ECP with or without IFN or systemic retinoids resulted in an ORR of 79% (CR in 26%) with a median OS of 74 months.[112] 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; however, these differences in outcomes were not statistically significant.[112] In a retrospective cohort study of patients with SS (n = 98) who received at least 3 months of

ECP combined with 1 or more biologic agents (ie, IFN alfa, systemic retinoid, IFN gamma, GM-CSF), the ORR was 75% with CR in 30% of patients.[113] Most patients in 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%.[113] 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.[113]

Systemic retinoids have also been studied in combination with IFN 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 erythrodermic CTCL and follicular MF.[114] In a phase II study in patients with CTCL (n = 22; all stages), oral bexarotene (at standard doses; 300 mg/m^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).[115] 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.[70,71] 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.[116] 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 duration >5 years in 17%). The median DFS and OS rates 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.[116]

Allogeneic Hematopoietic Cell Transplantation

Autologous hematopoietic stem cell transplantation (HCT) has been used infrequently for patients with CTCL. In general, the duration of response have been short, thus limiting its utility and uptake.[117] Allogeneic HCT for patients with advanced MF and SS has been reported in small prospective series or in retrospective studies.[118-122] In a multicenter retrospective analysis of 37 patients with advanced-stage primary CTCL treated with allogeneic HCT (24 patients [65%] had stage IV MFSS or disseminated nodal or visceral involvement), after a median follow-up of 29 months, the incidence of relapse was 56% and the estimated 2-year OS and PFS rates were 57% and 31%, respectively.[118] In a retrospective analysis of patients with advanced-stage MF/SS in the European Group for Blood and Marrow Transplantation (EBMT) database (n = 60) treated with allogeneic HCT, the 5-year PFS and OS rates were 32% and 46%, respectively. The corresponding 7-years survival rates were 44% and 30%, respectively.[119] The non-relapse mortality (NRM) rate at 7 years was 22%. Outcomes were not significantly different between histology types. However, patients with advanced-stage disease had an increased risk of relapse or progression as well as lower PFS and myeloablative conditioning was associated with poorer NRM and OS. In addition, transplants from unrelated donors had a statistically borderline impact on NRM and a significantly lower PFS as well as OS. In a prospective case series of 47 patients with advanced-stage MF/SS who underwent allogeneic HCT after failure of standard therapy, the estimated 4-year OS and PFS

rates were 51% and 26%, respectively.[121] While there was no statistical difference in the OS in patients who had MF alone, SS, MF with LCT, or SS with LCT, the 4-year PFS rate was superior in patients who had SS versus those who did not (52% vs. 10%; *P* = .02).

A meta-analysis compared the outcome of allogeneic versus autologous HCT in patients with MF and SS based on patient cases derived from the literature (n = 35).[123] The analysis suggested that OS outcomes and response durations were more favorable among the patients who received allogeneic HCT.[123] In the allogeneic HCT 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 HCT may be attributable to PD,[123] deaths associated with allogeneic HCT may be more due to NRM. The incidence of NRM in published reports with allogeneic HCT 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 treatment-related mortality (TRM) rate was 21%.

Allogeneic HCT 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 HCT in these patients.

Treatment Recommendations Based on Clinical Stage

The NCCN Guidelines panel recommends that patients diagnosed with MF/SS be treated at specialized centers with expertise in the management of this disease. Due to the rarity of the condition and the need for an individualized approach, referral to a multidisciplinary academic specialty center is preferred.

Primary Treatment

Stage IA Disease

Stage IA disease is managed primarily with skin-directed therapies, alone or in combination with other skin-directed therapies including local RT (8–12 Gy. 8 Gy may be given in a single-fraction Gy).[47,48] Local RT (24–30 Gy) is recommended particularly for unilesional presentation. Treatment options include topical corticosteroids, topical chemotherapy (mechlorethamine), topical retinoids (bexarotene or tazarotene), topical imiquimod, and/or phototherapy (UVB for patch or thin plaques; PUVA for thicker plaques) (see *Skin-Directed Therapies* in the algorithm on MFSS-A).

Stage IB-IIA Disease

Patients with stage IB-IIA disease require generalized skin treatment. In addition to the other skin-directed therapies used for stage IA disease (as mentioned above), TSEBT (12–36 Gy; 4 Gy per week) is another treatment option for those with severe skin symptoms or generalized thick plaque or tumor disease.[53,55] It is common practice to follow TSEBT with systemic therapies such as IFN or bexarotene to maintain response. Topical retinoids are not recommended for generalized skin involvement because these treatments can cause substantial irritation.

Stage IIB Disease

Patients with limited tumor disease can be managed with skin-directed therapies or systemic therapies (SYST-CAT A: retinoids, IFNs, HDAC inhibitors, ECP, methotrexate [≤100 mg per week], or brentuximab vedotin) with or without local RT for tumor 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 systemic biologic therapy (such as IFN or bexarotene) 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 (brentuximab vedotin, gemcitabine, liposomal doxorubicin, or low-dose pralatrexate are included as preferred regimens; chlorambucil, pentostatin, etoposide, cyclophosphamide, temozolomide, methotrexate [>100 mg per week], pembrolizumab, or bortezomib are included as other options), SYST-CAT C (bortezomib, brentuximab vedotin, gemcitabine, liposomal doxorubicin, low-dose or standard-dose pralatrexate, or romidepsin regimens are recommended for PTCL in the NCCN Guidelines for T-Cell Lymphomas), or combination therapies.

Stage III Disease

Management of patients with stage III disease depends on the extent of blood involvement. Stage III disease with no significant blood involvement (B0) should be managed with generalized skin-directed therapies similar to those recommended for stage IB-IIA disease. 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. TSEBT may not be well tolerated in patients with stage III disease and should be used with caution. In these patients, TSBET may be used with lower doses and slower fractionation.

Stage III disease with blood involvement (B1) should be managed with systemic therapy options listed under SYST-CAT A, with or without skin-directed therapy.

Stage IV Disease

Stage IV disease includes SS and non-Sézary or visceral (solid organ) disease. SS is treated with single-agent systemic therapy (agents listed in SYST-CAT A) or combination therapies. Safety data on the use of TSEBT in combination with systemic retinoids or HDAC inhibitors (vorinostat or romidepsin) are currently lacking. Non-Sézary or solid organ disease is frequently managed with systemic therapy (SYST-CAT B, SYST-CAT C, or multiagent chemotherapy) with or without RT for local control. Stage IV disease 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.

Additional Therapy Based on Response to Primary Treatment

Response criteria for MF/SS have not been demonstrated to correlate with prognosis. The decisions to continue with or switch treatment regimens are often made based on clinical parameters. Imaging with the same modalities used in workup is indicated when there is suspicion of disease progression or extracutaneous disease. A proposal for the standardization of definition of response in skin, nodes, blood, and viscera has been published.[7]

All patients (stage IA through stage IV) 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 responds well to the same treatment. 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 tumor 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 generalized disease should continue to receive

TSEBT, systemic therapies, or combination therapies, with or without skin-directed therapies.

PR or inadequate response should be treated with the other primary treatment options not received before to improve response before moving onto treatment for refractory disease.

Large-cell Transformed or Folliculotropic Mycosis Fungoides

Histologic evidence of FMF or LCT may be associated with higher risk of disease progression and skin disease may be less responsive to topical therapies. Among patients with LCT, advanced age, LCT at the time of initial diagnosis of MF, high levels of LDH, and CD30 expression <10% are associated with disease progression.[19] Recent studies have reported that in a subgroup of patients with early skin-limited disease, FMF has an indolent disease course and a favorable prognosis.[27,28] Patients with early-stage FMF may benefit from standard skin-directed therapies used for the treatment of early-stage MF.[124] In a report from the Dutch Cutaneous Lymphoma Group that evaluated the treatment outcomes in patients with FMF (203 patients; 84 patients with early-stage FMF, 102 patients with advanced-stage FMF, and 17 patients with extracutaneous FMF), treatment with topical steroids and phototherapy with UVB or PUVA were more effective in patients with early-stage FMF resulting in an ORR of 83% (28% CR), 83%, and 88%, respectively. Local RT, TSEBT, and PUVA combined with RT were more effective in patients with advanced-stage FMF resulting in an ORR of 100% (63% CR), 100% (59% CR), and 75% (5% CR), respectively.

Primary treatment as described for stage IIB disease could be considered in selected patients with histologic evidence of FMF (indolent/plaque FMF without evidence of LCT). Patients with refractory disease with multiple therapies or disease progression should initially be considered for options under SYST-CAT A before resorting to treatment options listed under SYST-CAT B or SYST-CAT C. Systemic therapy is the initial treatment for patients with LCT (see MFSS-6 and MFSS-A in the algorithm). If there is no evidence of aggressive growth, systemic therapies from SYST-CAT A or SYST-CAT B are appropriate. For LCT with aggressive growth, the guidelines recommend systemic therapy with options listed under SYST-CAT C. Combination regimens are generally reserved for patients with relapsed or refractory or extracutaneous disease.

Refractory or Progressive Disease

Participation in a clinical trial is recommended for all patients with relapsed disease or PD.

Stage IA-IIA Disease

Clinical trial or systemic therapy (single agent or combination therapy with regimens listed under SYST-CAT A) is recommended for patients with stage IA, IB-IIA disease that is progressive or refractory to multiple skin-directed therapies. 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), and single-agent systemic chemotherapy regimens listed under SYST-CAT B.

Stage IIB

Stage IIB limited tumor disease that is progressive or refractory to multiple previous therapies should be treated with TSEBT, systemic chemotherapy, or combination therapies—with or without skin-directed therapies. Adjuvant systemic therapy (SYST-CAT A) after TSEBT may be considered to improve response duration.

Stage IIB generalized tumor disease that is progressive or refractory to multiple previous therapies should be managed with multiagent

chemotherapy or clinical trial. Most patients are generally treated with multiple agents from SYST-CAT A or SYST-CAT B or with combination therapies before receiving multiagent chemotherapy.

Stage III

Combination therapy or clinical trial should be considered for stage III disease that is progressive or refractory to multiple previous therapies. If the disease remains refractory or progresses during second-line therapy, then clinical trial, systemic therapy with agents listed under SYST-CAT B, or alemtuzumab may be considered. Lower doses of SC alemtuzumab is associated with lower incidence of infectious complications.

Stage IV

SS that is progressive or refractory to multiple previous therapies should be managed with systemic therapy with agents listed under SYST-CAT B, alemtuzumab, or clinical trial. Clinical trial should be considered for patients with non-Sézary or visceral disease that is progressive or refractory to multiple previous therapies.

Indications for Allogeneic HCT

Currently there is no definitive treatment for advanced disease that can produce reliable durable remissions or curative results, other than possibly allogeneic HCT. Patients with relapsed disease or PD only in the skin should not be referred for transplant.

Allogeneic HCT may be considered for patients with stage IIB-IV disease that is progressive or refractory to primary treatment options. Appropriate patients (with 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 HCT. When appropriate, TSEBT may be considered as cytoreductive therapy before transplant.

The ideal timing for allogeneic HCT 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 HCT 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 HCT 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 HCT should not be a “last resort” option.

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.[125-127] Patients with MF/SS should be evaluated for pruritus at each visit. Other potential causes of pruritus (eg, 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.

The treatment of pruritus requires optimizing skin-directed and systemic treatments. Daily use of moisturizers and emollients are helpful in maintaining and protecting the skin barrier. Topical steroids (with or without occlusion) can be effective in managing the disease and accompanying pruritus in early-stage disease.[127,128] First-line options

with systemic therapies include antihistamines, the tricyclic antidepressant doxepin, or the anticonvulsant gabapentin.[129-131] In the second-line setting, systemic therapy with the neurokinin-1 receptor antagonist aprepitant,[132-134] the tetracyclic antidepressant mirtazapine, or selective serotonin reuptake inhibitors may be considered.[129,135] Treatment with the oral opioid receptor antagonist naltrexone may be considered if symptoms of pruritus do not resolve with the above agents.[136,137]

Prevention and Treatment of Infections

Infectious complications are frequent among patients with MF/SS, particularly cutaneous bacterial infections and cutaneous herpes viral infections (eg, HSV or HZV infections).[138] 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.[138] 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 CMV reactivation and preemptively treated with antivirals to avoid overt CMV disease (see *Monoclonal Antibody Therapy and Viral Reactivation* in algorithm).

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.

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.

References

1. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005;105:3768-3785. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15692063.

2. Criscione VD, Weinstock MA. Incidence of cutaneous T-cell lymphoma in the United States, 1973-2002. Arch Dermatol 2007;143:854-859. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17638728.

3. Bradford PT, Devesa SS, Anderson WF, Toro JR. Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases. Blood 2009;113:5064-5073. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19279331.

4. Teras LR, DeSantis CE, Cerhan JR, et al. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. CA Cancer J Clin 2016;66:443-459. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27618563.

5. U.S. National Library of Medicine Key MEDLINE® Indicators Available at: http://www.nlm.nih.gov/bsd/bsd_key.html.

6. Olsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110:1713-1722. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17540844.

7. Olsen EA, Whittaker S, Kim YH, et al. Clinical end points and response criteria in mycosis fungoides and Sezary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. J Clin Oncol 2011;29:2598-2607. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21576639.

8. Kim YH, Bishop K, Varghese A, Hoppe RT. Prognostic factors in erythrodermic mycosis fungoides and the Sezary syndrome. Arch Dermatol 1995;131:1003-1008. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7661601.

9. Kim YH, Chow S, Varghese A, Hoppe RT. Clinical characteristics and long-term outcome of patients with generalized patch and/or plaque (T2) mycosis fungoides. Arch Dermatol 1999;135:26-32. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9923777.

10. de Coninck EC, Kim YH, Varghese A, Hoppe RT. Clinical characteristics and outcome of patients with extracutaneous mycosis fungoides. J Clin Oncol 2001;19:779-784. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11157031.

11. Kim YH, Liu HL, Mraz-Gernhard S, et al. Long-term outcome of 525 patients with mycosis fungoides and Sezary syndrome: clinical prognostic factors and risk for disease progression. Arch Dermatol 2003;139:857-866. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12873880.

12. Vidulich KA, Talpur R, Bassett RL, Duvic M. Overall survival in erythrodermic cutaneous T-cell lymphoma: an analysis of prognostic factors in a cohort of patients with erythrodermic cutaneous T-cell lymphoma. Int J Dermatol 2009;48:243-252. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19261011.

13. Agar NS, Wedgeworth E, Crichton S, et al. Survival outcomes and prognostic factors in mycosis fungoides/Sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. J Clin Oncol 2010;28:4730-4739. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20855822.

14. Talpur R, Singh L, Daulat S, et al. Long-term outcomes of 1,263 patients with mycosis fungoides and Sezary syndrome from 1982 to 2009. Clin Cancer Res 2012;18:5051-5060. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22850569.

15. Alberti-Violetti S, Talpur R, Schlichte M, et al. Advanced-stage mycosis fungoides and Sezary syndrome: survival and response to treatment. Clin Lymphoma Myeloma Leuk 2015;15:e105-112. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25817937.

16. Scarisbrick JJ, Prince HM, Vermeer MH, et al. Cutaneous lymphoma international consortium study of outcome in advanced stages of mycosis fungoides and Sezary syndrome: Effect of specific prognostic markers on survival and development of a prognostic model. J Clin Oncol 2015;33:3766-3773. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26438120.

17. Arulogun SO, Prince HM, Ng J, et al. Long-term outcomes of patients with advanced-stage cutaneous T-cell lymphoma and large cell transformation. Blood 2008;112:3082-3087. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18647960.

18. Pulitzer M, Myskowski PL, Horwitz SM, et al. Mycosis fungoides with large cell transformation: clinicopathological features and prognostic factors. Pathology 2014;46:610-616. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25393251.

19. Talpur R, Sui D, Gangar P, et al. Retrospective analysis of prognostic factors in 187 cases of transformed mycosis fungoides. Clin Lymphoma Myeloma Leuk 2016;16:49-56. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26702474.

20. Diamandidou E, Colome-Grimmer M, Fayad L, et al. Transformation of mycosis fungoides/Sezary syndrome: clinical characteristics and prognosis. Blood 1998;92:1150-1159. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9694702.

21. Vergier B, de Muret A, Beylot-Barry M, et al. Transformation of mycosis fungoides: clinicopathological and prognostic features of 45 cases. French Study Group of Cutaneious Lymphomas. Blood 2000;95:2212-2218. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10733487.

22. Benner MF, Jansen PM, Vermeer MH, Willemze R. Prognostic factors in transformed mycosis fungoides: a retrospective analysis of 100 cases. Blood 2012;119:1643-1649. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22160616.

23. van Doorn R, Scheffer E, Willemze R. Follicular mycosis fungoides, a distinct disease entity with or without associated follicular mucinosis: a clinicopathologic and follow-up study of 51 patients. Arch Dermatol 2002;138:191-198. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11843638.

24. Gerami P, Rosen S, Kuzel T, et al. Folliculotropic mycosis fungoides: an aggressive variant of cutaneous T-cell lymphoma. Arch Dermatol 2008;144:738-746. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18559762.

25. Lehman JS, Cook-Norris RH, Weed BR, et al. Folliculotropic mycosis fungoides: single-center study and systematic review. Arch Dermatol 2010;146:607-613. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20566923.

26. Wieser I, Wang C, Alberti-Violetti S, et al. Clinical characteristics, risk factors and long-term outcome of 114 patients with folliculotropic mycosis fungoides. Arch Dermatol Res 2017;309:453-459. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28516243.

27. Hodak E, Amitay-Laish I, Atzmony L, et al. New insights into folliculotropic mycosis fungoides (FMF): A single-center experience. J Am Acad Dermatol 2016;75:347-355. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27245278.

28. van Santen S, Roach RE, van Doorn R, et al. Clinical staging and prognostic factors in folliculotropic mycosis fungoides. JAMA Dermatol 2016;152:992-1000. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27276223.

29. Kim EJ, Hess S, Richardson SK, et al. Immunopathogenesis and therapy of cutaneous T cell lymphoma. J Clin Invest 2005;115:798-812. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15841167.

30. Thurber SE, Zhang B, Kim YH, et al. T-cell clonality analysis in biopsy specimens from two different skin sites shows high specificity in the diagnosis of patients with suggested mycosis fungoides. J Am Acad Dermatol 2007;57:782-790. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17646032.

31. Zhang B, Beck AH, Taube JM, et al. Combined use of PCR-based TCRG and TCRB clonality tests on paraffin-embedded skin tissue in the differential diagnosis of mycosis fungoides and inflammatory dermatoses. J Mol Diagn 2010;12:320-327. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20203005.

32. Tsai EY, Taur A, Espinosa L, et al. Staging accuracy in mycosis fungoides and sezary syndrome using integrated positron emission tomography and computed tomography. Arch Dermatol 2006;142:577-584. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16702495.

33. Zackheim HS. Treatment of patch-stage mycosis fungoides with topical corticosteroids. Dermatol Ther 2003;16:283-287. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14686970.

34. Kim YH, Martinez G, Varghese A, Hoppe RT. Topical nitrogen mustard in the management of mycosis fungoides: update of the Stanford experience. Arch Dermatol 2003;139:165-173. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12588222.

35. Lessin SR, Duvic M, Guitart J, et al. Topical chemotherapy in cutaneous T-cell lymphoma: positive results of a randomized, controlled, multicenter trial testing the efficacy and safety of a novel mechlorethamine, 0.02%, gel in mycosis fungoides. JAMA Dermatol 2013;149:25-32. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23069814.

36. Breneman D, Duvic M, Kuzel T, et al. Phase 1 and 2 trial of bexarotene gel for skin-directed treatment of patients with cutaneous T-cell lymphoma. Arch Dermatol 2002;138:325-332. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11902983.

37. Heald P, Mehlmauer M, Martin AG, et al. Topical bexarotene therapy for patients with refractory or persistent early-stage cutaneous T-cell lymphoma: results of the phase III clinical trial. J Am Acad Dermatol 2003;49:801-815. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14576658.

38. Apisarnthanarax N, Talpur R, Ward S, et al. Tazarotene 0.1% gel for refractory mycosis fungoides lesions: an open-label pilot study. J Am Acad Dermatol 2004;50:600-607. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15034511.

39. Deeths MJ, Chapman JT, Dellavalle RP, et al. Treatment of patch and plaque stage mycosis fungoides with imiquimod 5% cream. J Am Acad Dermatol 2005;52:275-280. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15692473.

40. Coors EA, Schuler G, Von Den Driesch P. Topical imiquimod as treatment for different kinds of cutaneous lymphoma. Eur J Dermatol 2006;16:391-393. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16935796.

41. Martinez-Gonzalez MC, Verea-Hernando MM, Yebra-Pimentel MT, et al. Imiquimod in mycosis fungoides. Eur J Dermatol 2008;18:148-152. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18424373.

42. Lewis DJ, Byekova YA, Emge DA, Duvic M. Complete resolution of mycosis fungoides tumors with imiquimod 5% cream: a case series. J

Dermatolog Treat 2017;28:567-569. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28635518.

43. Micaily B, Miyamoto C, Kantor G, et al. Radiotherapy for unilesional mycosis fungoides. Int J Radiat Oncol Biol Phys 1998;42:361-364. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9788416.

44. Wilson LD, Kacinski BM, Jones GW. Local superficial radiotherapy in the management of minimal stage IA cutaneous T-cell lymphoma (Mycosis Fungoides). Int J Radiat Oncol Biol Phys 1998;40:109-115. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9422565.

45. Piccinno R, Caccialanza M, Cuka E, Recalcati S. Localized conventional radiotherapy in the treatment of Mycosis Fungoides: our experience in 100 patients. J Eur Acad Dermatol Venereol 2014;28:1040-1044. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23998331.

46. Neelis KJ, Schimmel EC, Vermeer MH, et al. Low-dose palliative radiotherapy for cutaneous B- and T-cell lymphomas. Int J Radiat Oncol Biol Phys 2009;74:154-158. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18834672.

47. Thomas TO, Agrawal P, Guitart J, et al. Outcome of patients treated with a single-fraction dose of palliative radiation for cutaneous T-cell lymphoma. Int J Radiat Oncol Biol Phys 2013;85:747-753. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22818412.

48. Specht L, Dabaja B, Illidge T, et al. Modern radiation therapy for primary cutaneous lymphomas: field and dose guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys 2015;92:32-39. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25863751.

49. Chinn DM, Chow S, Kim YH, Hoppe RT. Total skin electron beam therapy with or without adjuvant topical nitrogen mustard or nitrogen mustard alone as initial treatment of T2 and T3 mycosis fungoides. Int J Radiat Oncol Biol Phys 1999;43:951-958. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10192339.

50. Ysebaert L, Truc G, Dalac S, et al. Ultimate results of radiation therapy for T1-T2 mycosis fungoides (including reirradiation). Int J Radiat Oncol Biol Phys 2004;58:1128-1134. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15001254.

51. Harrison C, Young J, Navi D, et al. Revisiting low-dose total skin electron beam therapy in mycosis fungoides. Int J Radiat Oncol Biol Phys 2011;81:e651-657. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21489711.

52. Kamstrup MR, Gniadecki R, Iversen L, et al. Low-dose (10-Gy) total skin electron beam therapy for cutaneous T-cell lymphoma: an open clinical study and pooled data analysis. Int J Radiat Oncol Biol Phys 2015;92:138-143. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25863761.

53. Hoppe RT, Harrison C, Tavallaee M, et al. Low-dose total skin electron beam therapy as an effective modality to reduce disease burden in patients with mycosis fungoides: results of a pooled analysis from 3 phase-II clinical trials. J Am Acad Dermatol 2015;72:286-292. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25476993.

54. Kroeger K, Elsayad K, Moustakis C, et al. Low-dose total skin electron beam therapy for cutaneous lymphoma : Minimal risk of acute toxicities. Strahlenther Onkol 2017;193:1024-1030. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28785772.

55. Morris S, Scarisbrick J, Frew J, et al. The Results of Low-Dose Total Skin Electron Beam Radiation Therapy (TSEB) in Patients With Mycosis Fungoides From the UK Cutaneous Lymphoma Group. Int J Radiat Oncol Biol Phys 2017;99:627-633. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28843374.

56. Gathers RC, Scherschun L, Malick F, et al. Narrowband UVB phototherapy for early-stage mycosis fungoides. J Am Acad Dermatol

2002;47:191-197. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12140464.

57. Diederen PV, van Weelden H, Sanders CJ, et al. Narrowband UVB and psoralen-UVA in the treatment of early-stage mycosis fungoides: a retrospective study. J Am Acad Dermatol 2003;48:215-219. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12582391.

58. Querfeld C, Rosen ST, Kuzel TM, et al. Long-term follow-up of patients with early-stage cutaneous T-cell lymphoma who achieved complete remission with psoralen plus UV-A monotherapy. Arch Dermatol 2005;141:305-311. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15781671.

59. Ponte P, Serrao V, Apetato M. Efficacy of narrowband UVB vs. PUVA in patients with early-stage mycosis fungoides. J Eur Acad Dermatol Venereol 2010;24:716-721. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19929938.

60. Almohideb M, Walsh S, Walsh S, et al. Bath psoralen-ultraviolet A and narrowband ultraviolet B phototherapy as initial therapy for early-stage mycosis fungoides: A retrospective cohort of 267 cases at the University of Toronto. Clin Lymphoma Myeloma Leuk 2017;17:604-612. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28711574.

61. Hughes CF, Khot A, McCormack C, et al. Lack of durable disease control with chemotherapy for mycosis fungoides and Sezary syndrome: a comparative study of systemic therapy. Blood 2015;125:71-81. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25336628.

62. Zic JA, Stricklin GP, Greer JP, et al. Long-term follow-up of patients with cutaneous T-cell lymphoma treated with extracorporeal photochemotherapy. J Am Acad Dermatol 1996;35:935-945. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8959953.

63. Gottlieb SL, Wolfe JT, Fox FE, et al. Treatment of cutaneous T-cell lymphoma with extracorporeal photopheresis monotherapy and in combination with recombinant interferon alfa: a 10-year experience at a single institution. J Am Acad Dermatol 1996;35:946-957. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8959954.

64. Bisaccia E, Gonzalez J, Palangio M, et al. Extracorporeal photochemotherapy alone or with adjuvant therapy in the treatment of cutaneous T-cell lymphoma: a 9-year retrospective study at a single institution. J Am Acad Dermatol 2000;43:263-271. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10906649.

65. Talpur R, Demierre MF, Geskin L, et al. Multicenter photopheresis intervention trial in early-stage mycosis fungoides. Clin Lymphoma Myeloma Leuk 2011;11:219-227. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21575927.

66. Knobler R, Duvic M, Querfeld C, et al. Long-term follow-up and survival of cutaneous T-cell lymphoma patients treated with extracorporeal photopheresis. Photodermatol Photoimmunol Photomed 2012;28:250-257. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22971190.

67. Zic JA. The treatment of cutaneous T-cell lymphoma with photopheresis. Dermatol Ther 2003;16:337-346. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14686977.

68. Olsen EA. Interferon in the treatment of cutaneous T-cell lymphoma. Dermatol Ther 2003;16:311-321. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14686974.

69. Kaplan EH, Rosen ST, Norris DB, et al. Phase II study of recombinant human interferon gamma for treatment of cutaneous T-cell lymphoma. J Natl Cancer Inst 1990;82:208-212. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2104937.

70. Duvic M, Hymes K, Heald P, et al. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. J Clin Oncol 2001;19:2456-2471. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11331325.

71. Duvic M, Martin AG, Kim Y, et al. Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. Arch Dermatol 2001;137:581-593. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11346336.

72. Querfeld C, Rosen ST, Guitart J, et al. Comparison of selective retinoic acid receptor- and retinoic X receptor-mediated efficacy, tolerance, and survival in cutaneous t-cell lymphoma. J Am Acad Dermatol 2004;51:25-32. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15243520.

73. Olsen EA, Kim YH, Kuzel TM, et al. Phase IIB multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. J Clin Oncol 2007;25:3109-3115. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17577020.

74. Duvic M, Olsen EA, Breneman D, et al. Evaluation of the long-term tolerability and clinical benefit of vorinostat in patients with advanced cutaneous T-cell lymphoma. Clin Lymphoma Myeloma 2009;9:412-416. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19951879.

75. Piekarz RL, Frye R, Turner M, et al. Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma. J Clin Oncol 2009;27:5410-5417. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19826128.

76. Whittaker SJ, Demierre MF, Kim EJ, et al. Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. J Clin Oncol 2010;28:4485-4491. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20697094.

77. Kim EJ, Kim YH, Rook AH, et al. Clinically significant responses achieved with romidepsin across disease compartments in patients with cutaneous T-cell lymphoma. Leuk Lymphoma 2015:1-8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25791237.

78. Kennedy GA, Seymour JF, Wolf M, et al. Treatment of patients with advanced mycosis fungoides and Sezary syndrome with alemtuzumab. Eur J Haematol 2003;71:250-256. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12950233.

79. Lundin J, Hagberg H, Repp R, et al. Phase 2 study of alemtuzumab (anti-CD52 monoclonal antibody) in patients with advanced mycosis fungoides/Sezary syndrome. Blood 2003;101:4267-4272. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12543862.

80. Bernengo MG, Quaglino P, Comessatti A, et al. Low-dose intermittent alemtuzumab in the treatment of Sezary syndrome: clinical and immunologic findings in 14 patients. Haematologica 2007;92:784-794. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17550851.

81. Alinari L, Geskin L, Grady T, et al. Subcutaneous alemtuzumab for Sezary Syndrome in the very elderly. Leuk Res 2008;32:1299-1303. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18096224.

82. Querfeld C, Mehta N, Rosen ST, et al. Alemtuzumab for relapsed and refractory erythrodermic cutaneous T-cell lymphoma: a single institution experience from the Robert H. Lurie Comprehensive Cancer Center. Leuk Lymphoma 2009;50:1969-1976. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19860617.

83. de Masson A, Guitera P, Brice P, et al. Long-term efficacy and safety of alemtuzumab in advanced primary cutaneous T-cell lymphomas. Br J Dermatol 2014;170:720-724. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24438061.

84. Zackheim HS, Kashani-Sabet M, Hwang ST. Low-dose methotrexate to treat erythrodermic cutaneous T-cell lymphoma: results in twenty-nine patients. J Am Acad Dermatol 1996;34:626-631. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8601652.

85. Zackheim HS, Kashani-Sabet M, McMillan A. Low-dose methotrexate to treat mycosis fungoides: a retrospective study in 69

patients. J Am Acad Dermatol 2003;49:873-878. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14576667.

86. Duvic M, Talpur R, Wen S, et al. Phase II evaluation of gemcitabine monotherapy for cutaneous T-cell lymphoma. Clin Lymphoma Myeloma 2006;7:51-58. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16879770.

87. Marchi E, Alinari L, Tani M, et al. Gemcitabine as frontline treatment for cutaneous T-cell lymphoma: phase II study of 32 patients. Cancer 2005;104:2437-2441. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16216001.

88. Pellegrini C, Stefoni V, Casadei B, et al. Long-term outcome of patients with advanced-stage cutaneous T cell lymphoma treated with gemcitabine. Ann Hematol 2014;93:1853-1857. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24908331.

89. Foss FM, Ihde DC, Breneman DL, et al. Phase II study of pentostatin and intermittent high-dose recombinant interferon alfa-2a in advanced mycosis fungoides/Sezary syndrome. J Clin Oncol 1992;10:1907-1913. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1453206.

90. Tsimberidou AM, Giles F, Duvic M, et al. Phase II study of pentostatin in advanced T-cell lymphoid malignancies: update of an M.D. Anderson Cancer Center series. Cancer 2004;100:342-349. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14716770.

91. Tani M, Fina M, Alinari L, et al. Phase II trial of temozolomide in patients with pretreated cutaneous T-cell lymphoma. Haematologica 2005;90:1283-1284. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16154858.

92. Zinzani PL, Musuraca G, Tani M, et al. Phase II trial of proteasome inhibitor bortezomib in patients with relapsed or refractory cutaneous T-cell lymphoma. J Clin Oncol 2007;25:4293-4297. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17709797.

93. Horwitz SM, Kim YH, Foss F, et al. Identification of an active, well-tolerated dose of pralatrexate in patients with relapsed or refractory cutaneous T-cell lymphoma (CTCL). Blood 2012;119:4115-4122. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22394596.

94. Foss F, Horwitz SM, Coiffier B, et al. Pralatrexate is an effective treatment for relapsed or refractory transformed mycosis fungoides: a subgroup efficacy analysis from the PROPEL study. Clin Lymphoma Myeloma Leuk 2012;12:238-243. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22542448.

95. Talpur R, Thompson A, Gangar P, Duvic M. Pralatrexate alone or in combination with bexarotene: long-term tolerability in relapsed/refractory mycosis fungoides. Clin Lymphoma Myeloma Leuk 2014;14:297-304. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24589156.

96. Pulini S, Rupoli S, Goteri G, et al. Pegylated liposomal doxorubicin in the treatment of primary cutaneous T-cell lymphomas. Haematologica 2007;92:686-689. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17488695.

97. Quereux G, Marques S, Nguyen JM, et al. Prospective multicenter study of pegylated liposomal doxorubicin treatment in patients with advanced or refractory mycosis fungoides or Sezary syndrome. Arch Dermatol 2008;144:727-733. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18559761.

98. Dummer R, Quaglino P, Becker JC, et al. Prospective international multicenter phase II trial of intravenous pegylated liposomal doxorubicin monochemotherapy in patients with stage IIB, IVA, or IVB advanced mycosis fungoides: final results from EORTC 21012. J Clin Oncol 2012;30:4091-4097. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23045580.

99. Straus DJ, Duvic M, Horwitz SM, et al. Final results of phase II trial of doxorubicin HCl liposome injection followed by bexarotene in advanced cutaneous T-cell lymphoma. Annals of Oncology

2014;25:206-210. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24285015.

100. Duvic M, Tetzlaff MT, Gangar P, et al. Results of a phase II trial of brentuximab vedotin for CD30+ cutaneous T-cell lymphoma and lymphomatoid papulosis. J Clin Oncol 2015;33:3759-3765. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26261247.

101. Kim YH, Tavallaee M, Sundram U, et al. Phase II Investigator-Initiated Study of Brentuximab Vedotin in Mycosis Fungoides and Sezary Syndrome With Variable CD30 Expression Level: A Multi-Institution Collaborative Project. J Clin Oncol 2015;33:3750-3758. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26195720.

102. Prince HM, Kim YH, Horwitz SM, et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. Lancet 2017;390:555-566. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28600132.

103. Khodadoust M, Rook AH, Porcu P, et al. Pembrolizumab for treatment of relapsed/refractory mycosis fungoides and Sezary syndrome: Clinical efficacy in a CITN multicenter phase 2 study [abstract]. Blood 2016;128:Abstract 181. Available at: http://www.bloodjournal.org/content/128/22/181.abstract.

104. Roenigk HH, Jr., Kuzel TM, Skoutelis AP, et al. Photochemotherapy alone or combined with interferon alpha-2a in the treatment of cutaneous T-cell lymphoma. J Invest Dermatol 1990;95:198S-205S. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2258636.

105. Kuzel TM, Roenigk HH, Jr., Samuelson E, et al. Effectiveness of interferon alfa-2a combined with phototherapy for mycosis fungoides and the Sezary syndrome. J Clin Oncol 1995;13:257-263. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7799028.

106. Stadler R, Otte HG, Luger T, et al. Prospective randomized multicenter clinical trial on the use of interferon -2a plus acitretin versus interferon -2a plus PUVA in patients with cutaneous T-cell lymphoma stages I and II. Blood 1998;92:3578-3581. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9808550.

107. Chiarion-Sileni V, Bononi A, Fornasa CV, et al. Phase II trial of interferon-alpha-2a plus psolaren with ultraviolet light A in patients with cutaneous T-cell lymphoma. Cancer 2002;95:569-575. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12209749.

108. McGinnis KS, Shapiro M, Vittorio CC, et al. Psoralen plus long-wave UV-A (PUVA) and bexarotene therapy: An effective and synergistic combined adjunct to therapy for patients with advanced cutaneous T-cell lymphoma. Arch Dermatol 2003;139:771-775. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12810509.

109. Rupoli S, Goteri G, Pulini S, et al. Long-term experience with low-dose interferon-alpha and PUVA in the management of early mycosis fungoides. Eur J Haematol 2005;75:136-145. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16000130.

110. Whittaker S, Ortiz P, Dummer R, et al. Efficacy and safety of bexarotene combined with psoralen-ultraviolet A (PUVA) compared with PUVA treatment alone in stage IB-IIA mycosis fungoides: final results from the EORTC Cutaneous Lymphoma Task Force phase III randomized clinical trial (NCT00056056). Br J Dermatol 2012;167:678-687. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22924950.

111. Rupoli S, Canafoglia L, Goteri G, et al. Results of a prospective phase II trial with oral low-dose bexarotene plus photochemotherapy (PUVA) in refractory and/or relapsed patients with mycosis fungoides. Eur J Dermatol 2016;26:13-20. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26678311.

112. Suchin KR, Cucchiara AJ, Gottleib SL, et al. Treatment of cutaneous T-cell lymphoma with combined immunomodulatory therapy:

a 14-year experience at a single institution. Arch Dermatol 2002;138:1054-1060. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12164743.

113. Raphael BA, Shin DB, Suchin KR, et al. High clinical response rate of Sezary syndrome to immunomodulatory therapies: prognostic markers of response. Arch Dermatol 2011;147:1410-1415. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21844430.

114. McGinnis KS, Junkins-Hopkins JM, Crawford G, et al. Low-dose oral bexarotene in combination with low-dose interferon alfa in the treatment of cutaneous T-cell lymphoma: clinical synergism and possible immunologic mechanisms. J Am Acad Dermatol 2004;50:375-379. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14988678.

115. Straus DJ, Duvic M, Kuzel T, et al. Results of a phase II trial of oral bexarotene (Targretin) combined with interferon alfa-2b (Intron-A) for patients with cutaneous T-cell lymphoma. Cancer 2007;109:1799-1803. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17366595.

116. Duvic M, Apisarnthanarax N, Cohen DS, et al. Analysis of long-term outcomes of combined modality therapy for cutaneous T-cell lymphoma. J Am Acad Dermatol 2003;49:35-49. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12833006.

117. Duarte RF, Schmitz N, Servitje O, Sureda A. Haematopoietic stem cell transplantation for patients with primary cutaneous T-cell lymphoma. Bone Marrow Transplant 2008;41:597-604. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18176611.

118. de Masson A, Beylot-Barry M, Bouaziz JD, et al. Allogeneic stem cell transplantation for advanced cutaneous T-cell lymphomas: a study from the French Society of Bone Marrow Transplantation and French Study Group on Cutaneous Lymphomas. Haematologica 2014;99:527-534. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24213148.

119. Duarte RF, Boumendil A, Onida F, et al. Long-term outcome of allogeneic hematopoietic cell transplantation for patients with mycosis fungoides and Sezary syndrome: a European society for blood and marrow transplantation lymphoma working party extended analysis. J Clin Oncol 2014;32:3347-3348. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25154828.

120. Lechowicz MJ, Lazarus HM, Carreras J, et al. Allogeneic hematopoietic cell transplantation for mycosis fungoides and Sezary syndrome. Bone Marrow Transplant 2014;49:1360-1365. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25068422.

121. Hosing C, Bassett R, Dabaja B, et al. Allogeneic stem-cell transplantation in patients with cutaneous lymphoma: updated results from a single institution. Ann Oncol 2015;26:2490-2495. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26416896.

122. Shiratori S, Fujimoto K, Nishimura M, et al. Allogeneic hematopoietic stem cell transplantation following reduced-intensity conditioning for mycosis fungoides and Sezary syndrome. Hematol Oncol 2016;34:9-16. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25312300.

123. Wu PA, Kim YH, Lavori PW, et al. A meta-analysis of patients receiving allogeneic or autologous hematopoietic stem cell transplant in mycosis fungoides and Sezary syndrome. Biol Blood Marrow Transplant 2009;15:982-990. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19589488.

124. van Santen S, van Doorn R, Neelis KJ, et al. Recommendations for treatment in folliculotropic mycosis fungoides: report of the Dutch Cutaneous Lymphoma Group. Br J Dermatol 2017;177:223-228. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28132406.

125. Demierre MF, Gan S, Jones J, Miller DR. Significant impact of cutaneous T-cell lymphoma on patients' quality of life: results of a 2005 National Cutaneous Lymphoma Foundation Survey. Cancer

2006;107:2504-2511. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17048251.

126. Sampogna F, Frontani M, Baliva G, et al. Quality of life and psychological distress in patients with cutaneous lymphoma. Br J Dermatol 2009;160:815-822. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19120325.

127. Meyer N, Paul C, Misery L. Pruritus in cutaneous T-cell lymphomas: frequent, often severe and difficult to treat. Acta Derm Venereol 2010;90:12-17. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20107719.

128. Trautinger F, Knobler R, Willemze R, et al. EORTC consensus recommendations for the treatment of mycosis fungoides/Sezary syndrome. Eur J Cancer 2006;42:1014-1030. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16574401.

129. Demierre MF, Taverna J. Mirtazapine and gabapentin for reducing pruritus in cutaneous T-cell lymphoma. J Am Acad Dermatol 2006;55:543-544. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16908377.

130. Eschler DC, Klein PA. An evidence-based review of the efficacy of topical antihistamines in the relief of pruritus. J Drugs Dermatol 2010;9:992-997. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20684150.

131. Matsuda KM, Sharma D, Schonfeld AR, Kwatra SG. Gabapentin and pregabalin for the treatment of chronic pruritus. J Am Acad Dermatol 2016;75:619-625 e616. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27206757.

132. Duval A, Dubertret L. Aprepitant as an antipruritic agent? N Engl J Med 2009;361:1415-1416. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19797294.

133. Booken N, Heck M, Nicolay JP, et al. Oral aprepitant in the therapy of refractory pruritus in erythrodermic cutaneous T-cell lymphoma. Br J Dermatol 2011;164:665-667. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21039410.

134. Jimenez Gallo D, Albarran Planelles C, Linares Barrios M, et al. Treatment of pruritus in early-stage hypopigmented mycosis fungoides with aprepitant. Dermatol Ther 2014;27:178-182. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24517320.

135. Stander S, Bockenholt B, Schurmeyer-Horst F, et al. Treatment of chronic pruritus with the selective serotonin re-uptake inhibitors paroxetine and fluvoxamine: results of an open-labelled, two-arm proof-of-concept study. Acta Derm Venereol 2009;89:45-51. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19197541.

136. Metze D, Reimann S, Beissert S, Luger T. Efficacy and safety of naltrexone, an oral opiate receptor antagonist, in the treatment of pruritus in internal and dermatological diseases. J Am Acad Dermatol 1999;41:533-539. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10495371.

137. Bigliardi PL, Stammer H, Jost G, et al. Treatment of pruritus with topically applied opiate receptor antagonist. J Am Acad Dermatol 2007;56:979-988. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17320241.

138. Axelrod PI, Lorber B, Vonderheid EC. Infections complicating mycosis fungoides and Sezary syndrome. JAMA 1992;267:1354-1358. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1740857.

Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders

Overview

Primary cutaneous CD30+ T-cell lymphoproliferative disorders (PCTLD) represent a spectrum that includes primary cutaneous anaplastic large cell lymphoma (PC-ALCL), lymphomatoid papulosis (LyP), and "borderline" cases with overlapping clinical and histopathologic features.[1] Primary cutaneous disease, spontaneous regression, and absence of extracutaneous spread are associated with a better prognosis.[2,3]

PC-ALCL represents about 8% of all CTCL and is histologically characterized by diffuse, cohesive sheets of large CD30-positive (in >75%) cells with anaplastic, pleomorphic, or immunoblastic appearance.[1] Patches and plaques may also be present and some degree of spontaneous remittance in lesions may also be seen. PC-ALCL typically follows an indolent course with an excellent prognosis, although cutaneous relapses are more common.[4-6] 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.[5] The presence of extensive skin lesions on the leg and disease progression to extracutaneous disease are associated with poorer outcomes.[7,8]

LyP is histologically heterogenous with large atypical anaplastic, immunoblastic, or Hodgkin-like cells in a marked inflammatory background.[9] Several histologic subtypes (types A to D and other types, with CD30-positive cells) have been defined based on the evolution of skin lesions. Clinical features include chronic, recurrent, spontaneously regressing papulonodular (grouped or generalized) skin lesions. LyP is not considered a malignant disorder and has an excellent prognosis with an OS rate of 92% at 5 and 10 years.[6] However, LyP has also been reported to be associated with an increased risk of secondary lymphomas such as MF, PC-ALCL, systemic ALCL, or Hodgkin lymphoma.[10-15] Older age, positive *TCR* gene rearrangement, or diagnosis of mixed-type LyP have been reported as prognostic indicators of disease progression to lymphoma.[11,13]

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for T-Cell Lymphomas, an electronic search of the PubMed database was performed to obtain key literature in primary CD30+ cutaneous PCTLD published between May 2016 and December 2017 using the following search terms: primary cutaneous anaplastic large cell lymphoma (PC-ALCL) and LyP. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[16]

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 55 citations and their potential relevance was examined. The data from key PubMed articles selected by the panel for review during the Guidelines update meeting as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). 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 website.

Diagnosis

Clinical correlation with histopathologic features is essential for establishing the diagnosis of PCTLD. Diagnosis cannot be made based on pathology review alone. It is critical to distinguish CD30+ PCTLD from other cutaneous CD30+ disorders involving the skin, which include systemic ALCL, ATLL, PTCL, MF (especially transformed MF), and benign disorders such as lymphomatoid drug reactions, arthropod bites, viral infections, and others. MF and PCTLD can coexist in the same patient. Lymphomatoid drug reactions have been linked with certain drugs (eg, amlodipine, carbamazepine, cefuroxime, valsartan) and are associated with CD30+ atypical large cells in histology. Classical Hodgkin lymphoma (CHL) is less often associated with MF and PCTLD than previously thought; however, coexpression of CD30 and CD15 in these T-cell lymphomas may lead to a mistaken diagnosis of CHL.[17] It is therefore important not to diagnose CD30+ T-cell lymphomas in lymph nodes as Hodgkin's lymphoma.

Complete skin examination (for evidence of MF), adequate biopsy (punch, incisional, or excisional) of suspicious skin lesions, and immunohistochemical studies of skin biopsy are essential to confirm the diagnosis. Molecular analysis to detect *TCR* clonal gene rearrangements, excisional or incisional biopsy of suspicious lymph nodes, and assessment of HTLV-1 serology to identify CD30+ ATLL would be helpful in selected circumstances. However, *TCR* gene rearrangement may not be demonstrated in all cases of MF/SS. Demonstration of identical clones in skin, blood, and/or lymph nodes may be helpful in selected cases.[18]

PCTLD are characterized by the following immunophenotype: CD30+ (>75% cells), CD4+, variable loss of CD2/CD5/CD3, CD8+ (<5%) cytotoxic granule-associated proteins positive. The recommended immunophenotyping panel includes CD3, CD4, CD8, CD20, CD30, CD56, and ALK. ALK positivity and t(2;5) translocation is typically absent in CD30+ PCTLD and differential expression of t(2;5) can help to distinguish between CD30+ PCTLD and ALCL of nodal origin.[19] Additional markers such as CD2, CD5, CD7, CD25, TIA1, granzyme B, perforin, GM1, EBER-ISH, IRF4/MUM1, and EMA may be useful in selected circumstances. Abnormal T-cell phenotype and perforin expression are significantly more frequent in PC-ALCL than in transformed MF and may be useful for the differential diagnosis between PC-ALCL and CD30-expressing transformed MF.[20] MUM1 expression is valuable for the distinction between LyP and PC-ALCL, since the majority of cases of LyP (87%) are positive for MUM1 staining compared to only 20% of cases with PC-ALCL.[21] *DUSP22-IRF4* (6p25.3) gene rearrangement has been described in patients with PCALCL and LyP.[22-24] In a large multicenter study that investigated the clinical utility of detecting *IRF4* translocations in skin biopsies of T-cell lymphoproliferative disorders, FISH for *IRF4* had a specificity and positive predictive value of 99% and 90%, respectively, for cutaneous ALCL.[22] FISH to detect *DUSP22-IRF4* rearrangement would be useful in selected circumstances.

Workup

The initial workup involves a complete physical exam including entire skin, palpation of peripheral lymph node regions, and liver or spleen enlargement. Laboratory studies should include CBC with differential, a

comprehensive metabolic panel, and assessment of LDH levels. Biopsy of suspicious lymph nodes is recommended for PC-ALCL. Contrast-enhanced CT scan of the chest, abdomen, and pelvis or integrated whole body PET/CT is recommended for PC-ALCL. Bone marrow evaluation has limited value in the staging of patients with PC-ALCL and is not required for disease staging.[25] Bone marrow aspiration and biopsy is recommended only for solitary PC-ALCL or PC-ALCL with extracutaneous involvement on imaging. In LyP, imaging studies and bone marrow evaluation are done only if there is suspicion of systemic involvement by an associated lymphoma. Many skin-directed and systemic therapies are contraindicated or of unknown safety in pregnancy. Therefore, pregnancy testing is recommended for women of childbearing age.

Primary Treatment

For patients with PC-ALCL, ISRT alone or surgical excision with or without ISRT are recommended for patients with solitary or grouped lesions.[4-6,9,26-29]

In a report from the Dutch Cutaneous Lymphoma Group that evaluated the long-term outcome of 219 patients with PCTLD (118 patients with LyP, 79 patients with PC-ALCL, and 11 patients with PC-ALCL with regional node involvement), RT or surgical excision as initial therapy (given for 48% and 19% of patients, respectively) resulted in a CR rate of 100% in patients with PC-ALCL.[5] After a median follow-up of 61 months, subsequent skin-only relapse and extracutaneous disease were reported in 41% and 10% of patients, respectively. Among the 118 patients with LyP, topical steroids and phototherapy were the most common initial treatment given to 56% and 35% of patients, respectively.[5] Although CR or PR was common, none of these therapies resulted in sustained CR.

A more recent multicenter retrospective analysis restricted to patients with PC-ALCL (n = 56) eligible to receive RT (primary therapy or after surgical excision) reported a complete clinical response (CCR) rate of 95% and the local control rate was 98% after a median follow-up of 3.5 years.[30] Although the median RT dose was 35 Gy (range, 6–45 Gy) CRs were seen with doses as low as 6 Gy and the achievement of CCR was independent of the RT dose, suggesting that lower RT dose of <30 Gy may be appropriate for the management of localized lesions. The efficacy of low-dose RT (≤20 Gy) for the treatment of solitary or localized PC-ALCL was also confirmed in two other recent reports.[31,32]

When managing patients with LyP, it is important to be reminded that this is not a malignant disorder but a recurrent, benign, self-regressing lymphoid proliferation. Observation is preferred for asymptomatic disease. Topical steroids and phototherapy are the most commonly used initial treatment options for limited lesions.[5,33-36]

In a retrospective multicenter study of 252 patients with LyP, topical steroids and phototherapy were the most common first-line treatments (prescribed in 35% and 14% of the patients, respectively) resulting in a CR rate of 48%.[37] The overall estimated median DFS was 11 months but the DFS was longer for patients treated with phototherapy (23 months; $P < .03$). The presence of type A LyP and the use of first-line treatment other than phototherapy were significantly associated with increased risk of early cutaneous relapse.

Systemic therapy (brentuximab vedotin, methotrexate, pralatrexate, systemic retinoids, or IFN) is indicated only for multifocal lesions and for those with regional node involvement in patients with PC-ALCL and for extensive lesions in patients with LyP.

Low-dose methotrexate is widely used for the treatment of LyP.[37-45] In a retrospective study of 45 patients with LyP and other CD30+ PCTLD, low-dose methotrexate (≤25 mg) resulted in satisfactory disease control in 87% of patients, and the median total duration of treatment was >39 months for all patients.[40] After discontinuation, 25% of patients remained free of disease relapse during the follow-up period of 24 to 227 months. A more recent study that evaluated the efficacy of low-dose methotrexate in a cohort of 28 patients with LyP reported that satisfactory disease control could be achieved at 7.5- to 10-mg weekly doses of methotrexate.[45]

There are very limited data on the use of pralatrexate,[46] systemic retinoids,[35,47-49] and IFN [47,50-52] for PC-ALCL and LyP. Multiagent chemotherapy has also been studied in patients with PC-ALCL and LyP.[5,9,53] In the aforementioned report from the Dutch Cutaneous Lymphoma Group that evaluated the long-term outcome of 219 patients with PCTLD, 9 of 11 patients (82%) with PC-ALCL and regional node involvement received CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)-like multiagent chemotherapy as initial therapy (82%), resulting in a CR in 8 patients (88%).[5] However, 5 out of these 8 patients experienced skin relapses during follow-up. After a median follow-up of 58 months, disease-related 5-year survival rate was 91%. Although multiagent chemotherapy often leads to reduction or clearance of lesions, rapid recurrence shortly after or even during treatment is a consistent finding in patients with LyP.

Brentuximab vedotin is also safe and effective for the management of previously treated PC-ALCL and LyP.[54-56] In the ALCANZA study that included 31 patients with previously treated PC-ALCL, ORR lasting for ≥4 months was significantly higher for brentuximab vedotin compared to the physician's choice of treatment with methotrexate or bexarotene (75% vs. 20%), and the proportion of patients achieving CR was also higher with brentuximab vedotin than with physician's choice (31% vs. 7%).[55] In a phase II study of 12 patients with refractory LyP, brentuximab vedotin resulted in an ORR of 100% and a CR rate of 58%.[56] The median duration of response was 20 weeks. Grade 1 or 2 peripheral neuropathy was the most common adverse event reported in 10 patients (83%).Further studies are needed to optimize the dosing to minimize the incidences of peripheral neuropathy. For patients with PC-ALCL, brentuximab vedotin is the preferred systemic treatment option for patients with multifocal lesions and for patients with regional node involvement.

Follow-Up and Treatment for Relapsed/Refractory Disease

Regular follow-up (including complete skin exam) is essential during observation since these patients can develop MF over time. Life-long follow-up (including thorough skin exam) is warranted for patients with LyP (even for patients responding to initial treatment) due to high risks for second lymphoid malignancies.

Patients achieving a clinical benefit and/or those with disease responding to initial treatment should be considered for maintenance or tapering of regimens to optimize duration of response. PR should be treated with the other primary treatment options not received before to improve response before moving onto treatment for refractory disease. Disease relapse often responds well to the same treatment. In patients with PC-ALCL, refractory disease to multiple prior therapies should be managed with systemic therapy options (SYST-CAT C) recommended for MFSS. In patients with LyP, brentuximab vedotin is included as an option for disease that is refractory to multiple primary treatment options.

References

1. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016;127:2375-2390. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26980727.

2. Paulli M, Berti E, Rosso R, et al. CD30/Ki-1-positive lymphoproliferative disorders of the skin--clinicopathologic correlation and statistical analysis of 86 cases: a multicentric study from the European Organization for Research and Treatment of Cancer Cutaneous Lymphoma Project Group. J Clin Oncol 1995;13:1343-1354. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7751878.

3. Vergier B, Beylot-Barry M, Pulford K, et al. Statistical evaluation of diagnostic and prognostic features of CD30+ cutaneous lymphoproliferative disorders: a clinicopathologic study of 65 cases. Am J Surg Pathol 1998;22:1192-1202. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9777981.

4. Beljaards RC, Kaudewitz P, Berti E, et al. Primary cutaneous CD30-positive large cell lymphoma: definition of a new type of cutaneous lymphoma with a favorable prognosis. A European Multicenter Study of 47 patients. Cancer 1993;71:2097-2104. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8382999.

5. Bekkenk MW, Geelen FA, van Voorst Vader PC, et al. Primary and secondary cutaneous CD30(+) lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. Blood 2000;95:3653-3661. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10845893.

6. Liu HL, Hoppe RT, Kohler S, et al. CD30+ cutaneous lymphoproliferative disorders: the Stanford experience in lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma. J Am Acad Dermatol 2003;49:1049-1058. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14639383.

7. Woo DK, Jones CR, Vanoli-Storz MN, et al. Prognostic factors in primary cutaneous anaplastic large cell lymphoma: characterization of clinical subset with worse outcome. Arch Dermatol 2009;145:667-674. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19528422.

8. Benner MF, Willemze R. Applicability and prognostic value of the new TNM classification system in 135 patients with primary cutaneous anaplastic large cell lymphoma. Arch Dermatol 2009;145:1399-1404. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20026848.

9. Kempf W, Pfaltz K, Vermeer MH, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Blood 2011;118:4024-4035. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21841159.

10. Wang HH, Myers T, Lach LJ, et al. Increased risk of lymphoid and nonlymphoid malignancies in patients with lymphomatoid papulosis. Cancer 1999;86:1240-1245. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10506709.

11. de Souza A, el-Azhary RA, Camilleri MJ, et al. In search of prognostic indicators for lymphomatoid papulosis: a retrospective study of 123 patients. J Am Acad Dermatol 2012;66:928-937. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21982062.

12. Nikolaou V, Papadavid E, Ekonomidi A, et al. Association of clinicopathological characteristics with secondary neoplastic lymphoproliferative disorders in patients with lymphomatoid papulosis. Leuk Lymphoma 2015;56:1303-1307. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25242096.

13. Cordel N, Tressieres B, D'Incan M, et al. Frequency and Risk Factors for Associated Lymphomas in Patients With Lymphomatoid Papulosis. Oncologist 2016;21:76-83. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26668250.

14. Wieser I, Oh CW, Talpur R, Duvic M. Lymphomatoid papulosis: Treatment response and associated lymphomas in a study of 180 patients. J Am Acad Dermatol 2016;74:59-67. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26518172.

15. AbuHilal M, Walsh S, Shear N. Associated hematolymphoid malignancies in patients with lymphomatoid papulosis: A Canadian retrospective study. J Cutan Med Surg 2017;21:507-512. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28614957.

16. U.S. National Library of Medicine Key MEDLINE® Indicators Available at: http://www.nlm.nih.gov/bsd/bsd_key.html.

17. Eberle FC, Song JY, Xi L, et al. Nodal involvement by cutaneous CD30-positive T-cell lymphoma mimicking classical Hodgkin lymphoma. Am J Surg Pathol 2012;36:716-725. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22367293.

18. Thurber SE, Zhang B, Kim YH, et al. T-cell clonality analysis in biopsy specimens from two different skin sites shows high specificity in the diagnosis of patients with suggested mycosis fungoides. J Am Acad Dermatol 2007;57:782-790. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17646032.

19. DeCoteau JF, Butmarc JR, Kinney MC, Kadin ME. The t(2;5) chromosomal translocation is not a common feature of primary cutaneous CD30+ lymphoproliferative disorders: comparison with anaplastic large-cell lymphoma of nodal origin. Blood 1996;87:3437-3441. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8605362.

20. Fauconneau A, Pham-Ledard A, Cappellen D, et al. Assessment of diagnostic criteria between primary cutaneous anaplastic large-cell lymphoma and CD30-rich transformed mycosis fungoides; a study of 66 cases. Br J Dermatol 2015;172:1547-1554. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25645336.

21. Kempf W, Kutzner H, Cozzio A, et al. MUM1 expression in cutaneous CD30+ lymphoproliferative disorders: a valuable tool for the distinction between lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Br J Dermatol 2008;158:1280-1287. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18410414.

22. Wada DA, Law ME, Hsi ED, et al. Specificity of IRF4 translocations for primary cutaneous anaplastic large cell lymphoma: a multicenter study of 204 skin biopsies. Mod Pathol 2011;24:596-605. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21169992.

23. Karai LJ, Kadin ME, Hsi ED, et al. Chromosomal rearrangements of 6p25.3 define a new subtype of lymphomatoid papulosis. Am J Surg Pathol 2013;37:1173-1181. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23648461.

24. Onaindia A, Montes-Moreno S, Rodriguez-Pinilla SM, et al. Primary cutaneous anaplastic large cell lymphomas with 6p25.3 rearrangement exhibit particular histological features. Histopathology 2015;66:846-855. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25131361.

25. Benner MF, Willemze R. Bone marrow examination has limited value in the staging of patients with an anaplastic large cell lymphoma first presenting in the skin. Retrospective analysis of 107 patients. Br J Dermatol 2008;159:1148-1151. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18782320.

26. Yu JB, McNiff JM, Lund MW, Wilson LD. Treatment of primary cutaneous CD30+ anaplastic large-cell lymphoma with radiation therapy. Int J Radiat Oncol Biol Phys 2008;70:1542-1545. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18037577.

27. Booken N, Goerdt S, Klemke CD. Clinical spectrum of primary cutaneous CD30-positive anaplastic large cell lymphoma: an analysis of the Mannheim Cutaneous Lymphoma Registry. J Dtsch Dermatol Ges 2012;10:331-339. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22525148.

28. Huang BS, Chen WY, Wang CW, et al. Relapse pattern and treatment outcome of curative radiotherapy for primary cutaneous CD30+ anaplastic large-cell lymphoma: A retrospective cohort study. Acta Derm Venereol 2016;96:394-395. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26463467.

29. Hapgood G, Pickles T, Sehn LH, et al. Outcome of primary cutaneous anaplastic large cell lymphoma: a 20-year British Columbia Cancer Agency experience. Br J Haematol 2017;176:234-240. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27766622.

30. Million L, Yi EJ, Wu F, et al. Radiation therapy for primary cutaneous anaplastic large cell lymphoma: An International Lymphoma Radiation Oncology Group multi-institutional experience. Int J Radiat Oncol Biol Phys 2016;95:1454-1459. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27315663.

31. Melchers RC, Willemze R, Daniels LA, et al. Recommendations for the optimal radiation dose in patients with primary cutaneous anaplastic large cell lymphoma: A report of the Dutch Cutaneous Lymphoma Group. Int J Radiat Oncol Biol Phys 2017;99:1279-1285. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28958772.

32. Smith GL, Duvic M, Yehia ZA, et al. Effectiveness of low-dose radiation for primary cutaneous anaplastic large cell lymphoma. Adv Radiat Oncol 2017;2:363-369. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29114604.

33. Zackheim HS, Epstein EH, Jr., Crain WR. Topical carmustine therapy for lymphomatoid papulosis. Arch Dermatol 1985;121:1410-1414. Available at: https://www.ncbi.nlm.nih.gov/pubmed/4051529.

34. Thomsen K, Wantzin GL. Lymphomatoid papulosis. A follow-up study of 30 patients. J Am Acad Dermatol 1987;17:632-636. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2889756.

35. Krathen RA, Ward S, Duvic M. Bexarotene is a new treatment option for lymphomatoid papulosis. Dermatology 2003;206:142-147. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12592082.

36. Calzavara-Pinton P, Venturini M, Sala R. Medium-dose UVA1 therapy of lymphomatoid papulosis. J Am Acad Dermatol 2005;52:530-532. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15761440.

37. Fernandez-de-Misa R, Hernandez-Machin B, Servitje O, et al. First-line treatment in lymphomatoid papulosis: a retrospective multicentre study. Clin Exp Dermatol 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28994134.

38. Everett MA. Treatment of lymphomatoid papulosis with methotrexate. Br J Dermatol 1984;111:631. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6498098.

39. Christensen HK, Thomsen K, Vejlsgaard GL. Lymphomatoid papulosis: a follow-up study of 41 patients. Semin Dermatol 1994;13:197-201. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7986688.

40. Vonderheid EC, Sajjadian A, Kadin ME. Methotrexate is effective therapy for lymphomatoid papulosis and other primary cutaneous CD30-positive lymphoproliferative disorders. J Am Acad Dermatol 1996;34:470-481. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8609262.

41. Yazawa N, Kondo S, Kagaya M, et al. Successful treatment of a patient with lymphomatoid papulosis by methotrexate. J Dermatol 2001;28:373-378. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11510505.

42. Fujita H, Nagatani T, Miyazawa M, et al. Primary cutaneous anaplastic large cell lymphoma successfully treated with low-dose oral methotrexate. Eur J Dermatol 2008;18:360-361. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18474486.

43. Cornejo CM, Novoa RA, Krisch RE, Kim EJ. Low-dose radiotherapy for primary cutaneous anaplastic large-cell lymphoma while on low-dose methotrexate. Cutis 2016;98:253-256. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27874877.

44. Newland KM, McCormack CJ, Twigger R, et al. The efficacy of methotrexate for lymphomatoid papulosis. J Am Acad Dermatol 2015;72:1088-1090. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25981010.

45. Bruijn MS, Horvath B, van Voorst Vader PC, et al. Recommendations for treatment of lymphomatoid papulosis with methotrexate: a report from the Dutch Cutaneous Lymphoma Group. Br J Dermatol 2015;173:1319-1322. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25998985.

46. Horwitz SM, Kim YH, Foss F, et al. Identification of an active, well-tolerated dose of pralatrexate in patients with relapsed or refractory cutaneous T-cell lymphoma (CTCL). Blood 2012;119:4115-4122. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22394596.

47. Wyss M, Dummer R, Dommann SN, et al. Lymphomatoid papulosis--treatment with recombinant interferon alfa-2a and etretinate. Dermatology 1995;190:288-291. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7655107.

48. Sheehy O, Catherwood M, Pettengell R, Morris TC. Sustained response of primary cutaneous CD30 positive anaplastic large cell lymphoma to bexarotene and photopheresis. Leuk Lymphoma 2009;50:1389-1391. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19544141.

49. Fujimura T, Furudate S, Tanita K, et al. Successful control of phototherapy-resistant lymphomatoid papulosis with oral bexarotene. J Dermatol 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28971510.

50. Proctor SJ, Jackson GH, Lennard AL, Marks J. Lymphomatoid papulosis: response to treatment with recombinant interferon alfa-2b. J Clin Oncol 1992;10:170. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1727920.

51. Yagi H, Tokura Y, Furukawa F, Takigawa M. Th2 cytokine mRNA expression in primary cutaneous CD30-positive lymphoproliferative disorders: successful treatment with recombinant interferon-gamma. J Invest Dermatol 1996;107:827-832. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8941669.

52. Schmuth M, Topar G, Illersperger B, et al. Therapeutic use of interferon-alpha for lymphomatoid papulosis. Cancer 2000;89:1603-1610. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11013377.

53. Brice P, Cazals D, Mounier N, et al. Primary cutaneous large-cell lymphoma: analysis of 49 patients included in the LNH87 prospective trial of polychemotherapy for high-grade lymphomas. Groupe d'Etude des Lymphomes de l'Adulte. Leukemia 1998;12:213-219. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9519784.

54. Duvic M, Tetzlaff MT, Gangar P, et al. Results of a phase II trial of brentuximab vedotin for CD30+ cutaneous T-cell lymphoma and lymphomatoid papulosis. J Clin Oncol 2015;33:3759-3765. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26261247.

55. Prince HM, Kim YH, Horwitz SM, et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. Lancet 2017;390:555-566. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28600132.

56. Lewis DJ, Talpur R, Huen AO, et al. Brentuximab Vedotin for Patients With Refractory Lymphomatoid Papulosis: An Analysis of Phase 2 Results. JAMA Dermatol 2017;153:1302-1306. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28980004.

Adult T-Cell Leukemia/Lymphoma

Overview

Adult T Cell Leukemia/Lymphoma (ATLL) is malignancy of peripheral T-lymphocytes caused by 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).[1,2] 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.[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 = 1153).[3] ATLL was rare in North America or Europe (≤2%), but prevalent in Asia (25%), with all cases from Asia originating in Japan.

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 (eg, serum LDH, calcemia, lymphocytosis) and clinical features (eg, lymphadenopathy, hepatosplenomegaly, skin involvement).[4] The smoldering and chronic subtypes are considered indolent, usually characterized by ≥5% 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 also 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.[4] The chronic subtype is characterized by absolute lymphocytosis (≥4 x 10^9/L) with T-lymphocytes ≥3.5 x 10^9/L, normal calcium level, LDH levels within 2 times upper limit of normal, and no involvement of CNS, bone, or GI tract; lymphadenopathy and involvement of liver and spleen may be present.[4] The lymphoma subtype is characterized by the absence of lymphocytosis, ≤1% abnormal T-lymphocytes, and histologically proven lymphadenopathy with or without extranodal lesions. The acute subtype is associated with a rapidly PD course and usually presents with leukemic manifestation and tumor lesions, and represents cases that are not classified as any of the other 3 subtypes above.[4] The acute subtype is characterized by elevated LDH levels, hypercalcemia (with or without lytic bone lesions), B symptoms, generalized lymphadenopathy, splenomegaly, hepatomegaly, skin involvement, and organ infiltration.[5]

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for T-Cell Lymphomas, a literature search of the PubMed database was performed to obtain key literature in ATLL published between May 2016 and December 2017. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[6]

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 literature search resulted in 90 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 website.

Prognosis

The smoldering and chronic subtypes have a more favorable prognosis compared with the acute or the lymphoma subtypes. In the analysis of 818 patients with ATLL (median 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.[4] 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.[4] In a report from a long-term follow-up of 90 patients with newly diagnosed indolent ATLL, the median OS was 4 years and the estimated 5-, 10-, and 15-year survival rates were 47%, 25%, and 14%, respectively.[7] 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). 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. The acute and lymphoma subtypes can be associated with an aggressive disease course, with a median OS of 6 to 10 months.[3,8,9] The recent report from the ATL–Prognostic Index (ATL-PI) Project from Japan also confirmed the poor prognosis of acute and lymphoma subtypes with a median survival of 8 and 11 months, respectively, compared to 32 months and 55 months for chronic and smoldering subtypes.[9]

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.[10] Among patients with the chronic subtype, 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.[7] 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.[3] Based on univariate analysis, presence of B symptoms, platelet count $<150 \times 10^9$/L, and high IPI score (≥3) were found to be associated with decreased OS. However, in a multivariate analysis, IPI score was the only independent predictor for OS outcomes.[3]

New prognostic models have been proposed for patients since IPI scores are not always predictive of ATLL outcomes.[8,11] In a study based on the data from 89 patients with ATLL in North America (acute or lymphoma subtypes in 79%), the investigators proposed a new prognostic model that identified 3 prognostic categories based on ECOG performance status, Ann Arbor stage, age, and serum calcium level at diagnosis.[8] In a retrospective analysis of 807 patients newly diagnosed with acute- and lymphoma-type, Ann Arbor stage, ECOG performance status, and three continuous variables (age, serum albumin, and soluble interleukin-2 receptor [sIL-2R]) were identified as independent prognostic factors.[11] A prognostic model based on these variables stratified patients into 3 risk categories (low, intermediate, and high) with a median survival of 16.2 months, 7.3 months, and 3.6 months. A prognostic index for indolent ATLL (iATL-PI) has also been developed based on the sIL-2R levels.[11] In a retrospective analysis of 248 patients with chronic or smoldering ATLL, this prognostic index stratified patients into 3 risk groups (low risk, sIL-2R ≤1000 U/mL; intermediate risk, sIL-2R >1000 U/mL and ≤6000 U/mL; and high risk, sIL-2R >6000 U/mL). The median survival was not reached for patients with a low-risk score, whereas the median survival was 5.5 years and

1.6 years, respectively, for patients with an intermediate- or high-risk score. This prognostic index has to be validated in prospective trials.

Diagnosis

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%).[3] Bone marrow involvement (28%) and CNS involvement (10%) are also not uncommon.[3]

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.[12,13] 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.[4] The cytologic features of ATLL may be broad, but typical ATLL cells are characterized by so-called “flower cells,” which show distinct polylobate nuclei with homogeneous and condensed chromatin, small or absent nucleoli, and agranular and basophilic cytoplasm.[5,13] These cytologic characteristics are most evident in the acute subtype of the disease. HTLV-1 integration patterns have been reported to have clinical and prognostic implications for ATLL.[14] 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.

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 the GI tract should be performed. Excisional biopsy is recommended instead of core needle biopsy for the lymph nodes.[13] Biopsy of the suspicious lesion may also help to rule out certain underlying infections (eg, tuberculosis, histoplasmosis, toxoplasmosis). 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.[15]

If a biopsy is performed, the immunophenotyping panel should at minimum include the following markers: CD3, CD4, CD5, CD7, CD8, CD25, and CD30. 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.[5,13] Most ATLL cells lack CD7 and CD26 and have a dim CD3 expression.[13] Rare cases are CD8+ or CD4/CD8 double positive or double negative. In the Guidelines, the following is included as representative of a typical immunophenotype for ATLL: CD2+, CD3+, CD4+, CD7-, CD8-, CD25+, CD30-/+, TCR αβ+.

Workup

The initial workup for ATLL should include a complete history and 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 CBC with differential and complete metabolic panel (serum electrolyte levels, calcium, creatinine and blood urea nitrogen) and measurement of serum LDH levels. Measurement of serum uric acid

levels should be considered for patients with acute or lymphoma subtype since these are associated with a higher risk of developing spontaneous tumor lysis syndrome (TLS). *See Supportive Care: Tumor Lysis Syndrome* in the algorithm.

Upper GI tract endoscopy should be considered in selected cases since GI tract involvement is frequently observed in patients with aggressive ATLL.[16] 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 neurologic manifestations.[17]

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.[13] 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.[13]

The response is categorized as a 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), 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), SD (failure to achieve CR or PR with no PD), and relapsed disease or 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).[13] Each criterion for the response categories should be observed for a minimal period of 4 weeks to qualify for the response (eg, CR, PR, SD). The response criteria also include a category for CRu, 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

First-line Therapy

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

The activity of zidovudine in combination with IFN-alfa has been reported in a number of small studies and case reports.[18-22] Among patients with primarily treatment-naïve aggressive ATLL, zidovudine in combination with IFN-alfa resulted in ORR of 58% to 80% and CR rates of 20% to 50%.[18,19,22] Outcomes with this therapy were poorer for patients with previously treated relapsed/refractory disease, with ORR 17% to 67% (nearly all PRs).[20,21]

In a meta-analysis of 254 patients with ATLL, first-line therapy was composed of antiviral therapy (n = 75; comprising a combination of zidovudine and IFN-alfa in 97% of cases), chemotherapy alone (n = 77; CHOP in 86% of cases), or chemotherapy followed by maintenance antiviral therapy (n = 55).[23] Most of the patients (n = 207 evaluable) had acute (47%) or lymphoma (41%) subtypes, with the remaining patients presenting with indolent disease. 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.[23] 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%).[23] 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.[23] 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.[23] These data suggest that zidovudine in combination with IFN-alfa is effective in patients with leukemic ATLL, but not in the lymphoma subtype. A 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 IFN-alfa; given concurrent or sequential to chemotherapy or deferred).[24] 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.[24] 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.[24]

Combination chemotherapy with CHOP has resulted in an ORR of 64% to 88% (CR rates of 18% to 25%) with median OS ranging from about 8 to 12 months.[8,23,25] In a meta-analysis of 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.[23] 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 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* = .009).[23]

Several prospective studies have evaluated the role of more intensive combination chemotherapy regimens.[26-28]

A phase II multicenter study investigated the activity of CHOP followed by a regimen with vincristine, doxorubicin, cyclophosphamide, prednisolone, etoposide, vindesine, ranimustine, mitoxantrone, and

G-CSF (ATL-G-CSF) in patients with ATLL (n = 81).[26] The ORR 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%.[26] A randomized phase III trial conducted by JCOG compared VCAP-AMP-VECP with biweekly CHOP (CHOP-14) as first-line therapy for patients with aggressive ATLL (n = 118).[27] The CR rate was significantly higher with VCAP-AMP-VECP compared with CHOP-14 (40% vs. 25%; *P* = .02) but the 1-year progression-free survival (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.[27] The 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%).

In a small phase II trial conducted by the AIDS Malignancy Consortium in 19 patients with aggressive ATLL, EPOCH 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.[28] 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. In a more recent report, the use of dose-adjusted EPOCH in combination with bortezomib and antiviral therapy (raltegravir) resulted in an ORR of 67% in patients acute and lymphoma subtypes.[29] After a follow-up of >2 years, the median PFS and OS were both 6 months. In this study, no patients had dose-limiting toxicity, most likely due to the lower dose of cyclophosphamide at treatment initiation.

Hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) has also been reported to be an active regimen resulting in durable CRs in two patients with ATLL;[30] however, prospective evaluations are needed.

Relapsed/Refractory Disease

There are no effective treatment options since patients with ATLL have either been underrepresented or excluded from many clinical trials evaluating treatment options for relapsed/refractory T-cell lymphomas. Arsenic trioxide in combination with IFN-alfa has been shown to be an effective treatment option for relapsed or refractory disease despite significant toxicity.[31,32] Alemtuzumab, lenalidomide, bortezomib, and pralatrexate also have demonstrated activity as single agents in a small number of patients with relapsed/refractory ATLL.

In a phase II trial of 29 patients with chronic, acute, and lymphoma subtypes, alemtuzumab resulted in an objective ORR of 52% with a median response duration of 14.5 months among responders.[33] The median PFS and OS were 2 months and 6 months, respectively. CMV reactivation (responding to antiviral therapy) was observed in all patients.

In a phase II study that evaluated the efficacy and safety of lenalidomide in 26 patients with relapsed or refractory ATLL, lenalidomide resulted in an ORR of 42% and a tumor control rate of 73%.[34] The median PFS and OS were 4 months and 20 months, respectively. Neutropenia, leukopenia, lymphopenia, and thrombocytopenia were the most common grade ≥ 3 adverse events occurring in 65%, 38%, 38%, and 23% of patients, respectively.

Pralatrexate and bortezomib have limited activity in patients with relapsed/refractory ATLL resulting in an ORR of 19% and 7%,

respectively.[35,36] The risk of Stevens-Johnson syndrome may be higher in patients with ATLL compared to those with PTCL.[35] There are no data from prospective clinical trials on the use of HDAC inhibitors, belinostat and romidepsin) for the treatment of relapsed/refractory ATLL. In a small case series of patients with relapsed/refractory ATLL, romidepsin resulted in modest response rates and was also associated with higher rate of cytopenias.[37]

Mogamulizumab is a humanized monoclonal antibody approved for the treatment of patients with relapsed or refractory CCR4-positive ATLL in Japan.[38,39] The approval was based on the results of a multicenter phase II study for patients with relapsed, aggressive CCR4-positive ATLL (n = 28).[39] The primary endpoint of the trial was ORR; the secondary endpoints included PFS and OS outcomes. Patients were treated with mogamulizumab (1 mg/kg once per week for 8 weeks). 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%). Updated follow-up analysis from the phase I and II studies also confirmed the activity of mogamulizumab in patients with relapsed or refractory CCR4-positive ATLL.[40] Mogamulizumab is an investigational agent in the United States and has not been approved for any indication by the FDA. This agent is currently being evaluated in patients previously treated with ATLL in a multicenter, open-label, randomized study in the United States and elsewhere.

Allogeneic Hematopoietic Cell Transplantation

HCT has been shown to improve survival outcomes for some patients with ATLL,[41-46] suggesting a contribution of graft-versus-leukemia/lymphoma (GVL) effect.[47-49]

In a multicenter retrospective analysis that evaluated outcomes in patients with aggressive ATLL who received myeloablative allogeneic HCT (n = 40), the median OS for all patients following transplant was about 10 months.[43] Acute GVHD developed in 67% of patients. The estimated 3-year RFS and OS rates were 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%).[43] A large retrospective analysis was conducted in patients with ATLL who underwent allogeneic HCT (related or unrelated) (n = 386).[46] 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 a CR at the time of transplant, and the use of unrelated or cord blood were identified as adverse prognostic factors for OS outcomes.[46]

Allogeneic HCT using reduced-intensity conditioning (RIC) regimens has also been evaluated in an effort to reduce the high rate of TRM.[44,45,50] In a combined analysis from two prospective clinical trials (n = 29), the 5-year OS rate with RIC allogeneic HCT was 34%.[45] The NRM rate was 27.5%; 11 patients died due to disease progression. Ten patients were alive at a median follow-up of 82 months following transplant.[45]

In a retrospective study of 586 patients with ATLL (majority of patients had either acute [57%] or lymphoma [28%] subtypes), the use of myeloablative conditioning or RIC regimens resulted in similar outcomes with allogeneic HCT.[50] Patients who received RIC regimens were older than those who received myeloablative conditioning regimens (median age 57 years vs. 49 years). The median OS (survival measured from time of HCT) and 3-year OS rate was 9.5 months and 39%, respectively, among patients who received

myeloablative conditioning. The median OS and 3-year OS rate was 10 months and 34%, respectively, for patients who received RIC regimens. The 3-year cumulative incidence of TRM and ATLL-related death were 38% and 22.5%, respectively, for myeloablative conditioning regimens. The corresponding 3-year cumulative incidence rates for TRM and ATLL-related death were both 33% for RIC regimens. In the multivariate analysis, older age (>55 years), male sex, lack of CR at time of HCT, poorer performance status (PS ≥1), and unrelated donor HCT were significant independent factors for decreased OS outcomes. Male sex, poorer performance status (PS ≥1), and unrelated donor HCT were significant independent factors for risk of TRM.[50] 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 regimens. This analysis suggested that allogeneic HCT may offer long-term survival in some patients with ATLL.

Donor lymphocyte infusion (DLI) has been shown to induce long-term remissions in a few patients with PD or disease relapse after allogeneic HCT.[51] In a retrospective analysis of 35 patients with disease progression or disease relapse after first allogeneic HCT, among the patients who subsequently received DLI (n = 9), the median OS after relapse or 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.[51] 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.[51] This analysis showed that induction of GVL effect via DLI may provide long-lasting remission in selected patients with relapsed ATLL. However, prospective clinical trials are needed to confirm these findings.

HCT-specific comorbidity index (HCT-CI) and EBMT risk score have been considered as prognostic factors in patients with ATLL receiving allogeneic HCT.[52] An optimized prognostic index (ATL-HCT-PI; based on age, HCT-CI, and donor-recipient sex) has been recently developed for predicting NRM in patients receiving HCT.[53]

Prospective studies in larger groups of patients are warranted to further evaluate the role of allogeneic HCT and validate the use of ATL-HCT-PI in the management of patients with ATLL.

NCCN Recommendations

In the NCCN Guidelines, patients with ATLL are classified into 4 subtypes (chronic, smoldering, acute, and lymphoma) according to the Shimoyama criteria.[4] 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. PJP prophylaxis with sulfamethoxazole/trimethoprim or equivalent and screening and treatment (if needed) for strongyloidiasis are recommended for all patients.[13]

First-line Therapy

Observation is appropriate for patients with asymptomatic chronic or smoldering ATLL since both of these subtypes are considered indolent. Alternatively, if symptoms are present, these patients can be managed with skin-directed therapies for skin lesions (as recommend for patients with MF or SS within these NCCN Guidelines for T-Cell Lymphomas) as clinically indicated, or zidovudine in combination with IFN-alfa. Combination chemotherapy or zidovudine in combination with IFN-alfa

are included as treatment options for patients with acute ATLL. Combination chemotherapy (as mentioned above for acute ATLL) is recommended for patients with the lymphoma subtype. Zidovudine in combination with IFN-alfa is not considered effective for this group of patients.[23] CNS prophylaxis (with intrathecal methotrexate and cytarabine and corticosteroids) is recommended in patients with lymphoma subtype.

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

No standard treatment has been defined for patients with acute or lymphoma subtype and the efficacy of long-term treatment is limited. In the recent report from the ATL-PI Project from Japan that included 1250 patients with acute or lymphoma subtype, CHOP-like regimen (CHOP-21 or CHOP-14) was the most commonly used treatment (n = 579; 50%) followed by VCAP-AMP-VECP (n = 365; 31%), ATL-G-CSF (n = 56; 5%), and modified EPOCH (n = 42; 4%).[9] The chemotherapy regimens listed in the NCCN Guidelines (CHOP, CHOEP, dose-adjusted EPOCH, or hyper-CVAD) are based on institutional preferences and limited available data (mostly from retrospective analyses) as discussed above.[8,23,25,28-30] VCAP-AMP-VECP and ATL-G-CSF are not included since vindesine and ranimustine are not available in the United States.

Response Assessment and Additional Therapy

Continuation of the prior therapy is recommended for all patients who achieve an initial response to first-line systemic therapy (CR, uncertified PR, or PR at 2 months following start of treatment). Allogeneic HCT should be considered for patients with acute or lymphoma subtype, if donor is available.

For patients with chronic or smoldering subtype that is not responding to initial therapy (persistent disease or has disease progression at 2 months from start of treatment), options for additional therapy include combination chemotherapy regimens (as recommended for primary therapy for acute or lymphoma subtypes) or best supportive care. Patients with acute ATLL that is not responding to initial therapy should be treated with an alternate regimen not previously used for first-line therapy for ATLL or best supportive care. Second-line therapy or best supportive care are included as options for patients with lymphoma subtype that is not responding to initial therapy. In patients with acute or lymphoma subtypes who achieve a response to second-therapy, allogeneic HSCT should be considered if a donor is available.

The optimal second-line chemotherapy regimen is not yet established. Clinical trial is the preferred treatment option for all patients with relapsed/refractory disease. Regimens that are used for the treatment of relapsed/refractory PTCL are often applied to the treatment of relapsed or refractory ATLL, as there are limited data for this subtype. The regimens listed in the NCCN Guidelines are based on institutional preferences. Lenalidomide, alemtuzumab, bortezomib, and pralatrexate are included as monotherapy options based on limited available data as discussed above. Patients receiving alemtuzumab should be closely monitored and managed for potential development of CMV reactivation. *See Supportive Care: Monoclonal Antibody Therapy and Viral Reactivation* in the algorithm. CD30 expression has been reported at variable frequencies in ATLL subtypes with a trend towards a higher frequency of CD30 expression in lymphoma subtype compared to acute

subtype.[54] Brentuximab vedotin in included as an option for patients with CD30-positive relapsed/refractory disease.

References

1. Goncalves DU, Proietti FA, Ribas JG, et al. Epidemiology, treatment, and prevention of human T-cell leukemia virus type 1-associated diseases. Clin Microbiol Rev 2010;23:577-589. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20610824.

2. Ishitsuka K, Tamura K. Human T-cell leukaemia virus type I and adult T-cell leukaemia-lymphoma. Lancet Oncol 2014;15:e517-526. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25281470.

3. Suzumiya J, Ohshima K, Tamura K, et al. The International Prognostic Index predicts outcome in aggressive adult T-cell leukemia/lymphoma: analysis of 126 patients from the International Peripheral T-Cell Lymphoma Project. Ann Oncol 2009;20:715-721. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19150954.

4. Shimoyama M. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the Lymphoma Study Group (1984-87). Br J Haematol 1991;79:428-437. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1751370.

5. Ohshima K, Jaffe ES, Kikuchi M. Adult T-cell leukemia/lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:281-284.

6. U.S. National Library of Medicine Key MEDLINE® Indicators Available at: http://www.nlm.nih.gov/bsd/bsd_key.html.

7. Takasaki Y, Iwanaga M, Imaizumi Y, et al. Long-term study of indolent adult T-cell leukemia-lymphoma. Blood 2010;115:4337-4343. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20348391.

8. Phillips AA, Shapira I, Willim RD, et al. A critical analysis of prognostic factors in North American patients with human T-cell lymphotropic virus type-1-associated adult T-cell leukemia/lymphoma: a multicenter clinicopathologic experience and new prognostic score. Cancer 2010;116:3438-3446. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20564100.

9. Katsuya H, Ishitsuka K, Utsunomiya A, et al. Treatment and survival among 1594 patients with ATL. Blood 2015;126:2570-2577. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26361794.

10. Major prognostic factors of patients with adult T-cell leukemia-lymphoma: a cooperative study. Lymphoma Study Group (1984-1987). Leuk Res 1991;15:81-90. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2016910.

11. Katsuya H, Yamanaka T, Ishitsuka K, et al. Prognostic index for acute- and lymphoma-type adult T-cell leukemia/lymphoma. J Clin Oncol 2012;30:1635-1640. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22473153.

12. Tsukasaki K, Imaizumi Y, Tawara M, et al. Diversity of leukaemic cell morphology in ATL correlates with prognostic factors, aberrant immunophenotype and defective HTLV-1 genotype. Br J Haematol 1999;105:369-375. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10233406.

13. Tsukasaki K, Hermine O, Bazarbachi A, et al. Definition, prognostic factors, treatment, and response criteria of adult T-cell leukemia-lymphoma: a proposal from an international consensus meeting. J Clin Oncol 2009;27:453-459. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19064971.

14. Tsukasaki K, Tsushima H, Yamamura M, et al. Integration patterns of HTLV-I provirus in relation to the clinical course of ATL: frequent clonal change at crisis from indolent disease. Blood 1997;89:948-956. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9028326.

15. Takasaki Y, Iwanaga M, Tsukasaki K, et al. Impact of visceral involvements and blood cell count abnormalities on survival in adult T-cell leukemia/lymphoma (ATLL). Leuk Res 2007;31:751-757. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17188352.

16. Utsunomiya A, Hanada S, Terada A, et al. Adult T-cell leukemia with leukemia cell infiltration into the gastrointestinal tract. Cancer 1988;61:824-828. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3257406.

17. Teshima T, Akashi K, Shibuya T, et al. Central nervous system involvement in adult T-cell leukemia/lymphoma. Cancer 1990;65:327-332. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2295055.

18. Gill PS, Harrington W, Kaplan MH, et al. Treatment of adult T-cell leukemia-lymphoma with a combination of interferon alfa and zidovudine. N Engl J Med 1995;332:1744-1748. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7760890.

19. Bazarbachi A, Hermine O. Treatment with a combination of zidovudine and alpha-interferon in naive and pretreated adult T-cell leukemia/lymphoma patients. J Acquir Immune Defic Syndr Hum Retrovirol 1996;13 Suppl 1:186-190. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8797722.

20. Matutes E, Taylor GP, Cavenagh J, et al. Interferon alpha and zidovudine therapy in adult T-cell leukaemia lymphoma: response and outcome in 15 patients. Br J Haematol 2001;113:779-784. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11380470.

21. White JD, Wharfe G, Stewart DM, et al. The combination of zidovudine and interferon alpha-2B in the treatment of adult T-cell leukemia/lymphoma. Leuk Lymphoma 2001;40:287-294. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11426550.

22. Hermine O, Allard I, Levy V, et al. A prospective phase II clinical trial with the use of zidovudine and interferon-alpha in the acute and lymphoma forms of adult T-cell leukemia/lymphoma. Hematol J 2002;3:276-282. Available at: http://www.ncbi.nlm.nih.gov/PubMed/12522449.

23. Bazarbachi A, Plumelle Y, Carlos Ramos J, et al. Meta-analysis on the use of Zidovudine and interferon-alfa in adult T-cell leukemia/lymphoma showing improved survival in the leukemic subtypes. J Clin Oncol 2010;28:4177-4183. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20585095.

24. Hodson A, Crichton S, Montoto S, et al. Use of Zidovudine and Interferon Alfa With Chemotherapy Improves Survival in Both Acute and Lymphoma Subtypes of Adult T-Cell Leukemia/Lymphoma. J Clin Oncol 2011;29:4696-4701. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22042945.

25. Besson C, Panelatti G, Delaunay C, et al. Treatment of adult T-cell leukemia-lymphoma by CHOP followed by therapy with antinucleosides, alpha interferon and oral etoposide. Leuk Lymphoma 2002;43:2275-2279. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12613513.

26. Taguchi H, Kinoshita KI, Takatsuki K, et al. An intensive chemotherapy of adult T-cell leukemia/lymphoma: CHOP followed by etoposide, vindesine, ranimustine, and mitoxantrone with granulocyte colony-stimulating factor support. J Acquir Immune Defic Syndr Hum Retrovirol 1996;12:182-186. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8680890.

27. Tsukasaki K, Utsunomiya A, Fukuda H, et al. VCAP-AMP-VECP compared with biweekly CHOP for adult T-cell leukemia-lymphoma: Japan Clinical Oncology Group Study JCOG9801. J Clin Oncol 2007;25:5458-5464. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17968021.

28. Ratner L, Harrington W, Feng X, et al. Human T-cell leukemia virus reactivation with progression of adult T-cell leukemia-lymphoma. PLoS ONE 2009;4:e4420. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19204798.

29. Ratner L, Rauch D, Abel H, et al. Dose-adjusted EPOCH chemotherapy with bortezomib and raltegravir for human T-cell

leukemia virus-associated adult T-cell leukemia lymphoma. Blood Cancer J 2016;6:e408. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27015285.

30. Alduaij A, Butera JN, Treaba D, Castillo J. Complete remission in two cases of adult T-cell leukemia/lymphoma treated with hyper-CVAD: a case report and review of the literature. Clin Lymphoma Myeloma Leuk 2010;10:480-483. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21156467.

31. Hermine O, Dombret H, Poupon J, et al. Phase II trial of arsenic trioxide and alpha interferon in patients with relapsed/refractory adult T-cell leukemia/lymphoma. Hematol J 2004;5:130-134. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15048063.

32. Ishitsuka K, Suzumiya J, Aoki M, et al. Therapeutic potential of arsenic trioxide with or without interferon-alpha for relapsed/refractory adult T-cell leukemia/lymphoma. Haematologica 2007;92:719-720. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17488707.

33. Sharma K, Janik JE, O'Mahony D, et al. Phase II Study of Alemtuzumab (CAMPATH-1) in Patients with HTLV-1-Associated Adult T-cell Leukemia/lymphoma. Clin Cancer Res 2017;23:35-42. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27486175.

34. Ishida T, Fujiwara H, Nosaka K, et al. Multicenter Phase II Study of Lenalidomide in Relapsed or Recurrent Adult T-Cell Leukemia/Lymphoma: ATLL-002. J Clin Oncol 2016;34:4086-4093. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27621400.

35. Lunning MA, Gonsky J, Ruan J, et al. Pralatrexate in Relapsed/Refractory HTLV-1 Associated Adult T-Cell Lymphoma/Leukemia: A New York City Multi-Institutional Experience. Blood 2012;120:2735. Available at: http://www.bloodjournal.org/content/120/21/2735.abstract.

36. Ishitsuka K, Utsunomiya A, Katsuya H, et al. A phase II study of bortezomib in patients with relapsed or refractory aggressive adult T-cell leukemia/lymphoma. Cancer Sci 2015;106:1219-1223. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26179770.

37. Mukhi N, Verma V, Ahmed A, et al. Romidepsin in Relapsed/Refractory HTLV-1 Associated Adult T-Cell Lymphoma/Leukemia: A Case Series. Blood 2015;126:5113. Available at: http://www.bloodjournal.org/content/126/23/5113.abstract.

38. Yamamoto K, Utsunomiya A, Tobinai K, et al. Phase I study of KW-0761, a defucosylated humanized anti-CCR4 antibody, in relapsed patients with adult T-cell leukemia-lymphoma and peripheral T-cell lymphoma. J Clin Oncol 2010;28:1591-1598. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20177026.

39. Ishida T, Joh T, Uike N, et al. Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma: a multicenter phase II study. J Clin Oncol 2012;30:837-842. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22312108.

40. Ishida T, Utsunomiya A, Jo T, et al. Mogamulizumab for relapsed adult T-cell leukemia-lymphoma: Updated follow-up analysis of phase I and II studies. Cancer Sci 2017;108:2022-2029. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28776876.

41. Utsunomiya A, Miyazaki Y, Takatsuka Y, et al. Improved outcome of adult T cell leukemia/lymphoma with allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 2001;27:15-20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11244433.

42. Kami M, Hamaki T, Miyakoshi S, et al. Allogeneic haematopoietic stem cell transplantation for the treatment of adult T-cell leukaemia/lymphoma. Br J Haematol 2003;120:304-309. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12542491.

43. Fukushima T, Miyazaki Y, Honda S, et al. Allogeneic hematopoietic stem cell transplantation provides sustained long-term survival for patients with adult T-cell leukemia/lymphoma. Leukemia

2005;19:829-834. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15744352.

44. Okamura J, Uike N, Utsunomiya A, Tanosaki R. Allogeneic stem cell transplantation for adult T-cell leukemia/lymphoma. Int J Hematol 2007;86:118-125. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17875524.

45. Choi I, Tanosaki R, Uike N, et al. Long-term outcomes after hematopoietic SCT for adult T-cell leukemia/lymphoma: results of prospective trials. Bone Marrow Transplant 2010;46:116-118. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20400987.

46. Hishizawa M, Kanda J, Utsunomiya A, et al. Transplantation of allogeneic hematopoietic stem cells for adult T-cell leukemia: a nationwide retrospective study. Blood 2010;116:1369-1376. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20479287.

47. Shiratori S, Yasumoto A, Tanaka J, et al. A retrospective analysis of allogeneic hematopoietic stem cell transplantation for adult T cell leukemia/lymphoma (ATL): clinical impact of graft-versus-leukemia/lymphoma effect. Biol Blood Marrow Transplant 2008;14:817-823. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18541202.

48. Yonekura K, Utsunomiya A, Takatsuka Y, et al. Graft-versus-adult T-cell leukemia/lymphoma effect following allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 2008;41:1029-1035. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18332910.

49. Ishida T, Hishizawa M, Kato K, et al. Impact of graft-versus-host disease on allogeneic hematopoietic cell transplantation for adult T cell leukemia-lymphoma focusing on preconditioning regimens: nationwide retrospective study. Biol Blood Marrow Transplant 2013;19:1731-1739. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24090597.

50. Ishida T, Hishizawa M, Kato K, et al. Allogeneic hematopoietic stem cell transplantation for adult T-cell leukemia-lymphoma with special emphasis on preconditioning regimen: a nationwide retrospective study. Blood 2012;120:1734-1741. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22689862.

51. Itonaga H, Tsushima H, Taguchi J, et al. Treatment of relapsed adult T-cell leukemia/lymphoma after allogeneic hematopoietic stem cell transplantation: the Nagasaki Transplant Group experience. Blood 2013;121:219-225. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23100309.

52. Tokunaga M, Uto H, Takeuchi S, et al. Newly identified poor prognostic factors for adult T-cell leukemia-lymphoma treated with allogeneic hematopoietic stem cell transplantation. Leuk Lymphoma 2017;58:37-44. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27654808.

53. Yoshimitsu M, Tanosaki R, Kato K, et al. Risk Assessment in Adult T Cell Leukemia/Lymphoma Treated with Allogeneic Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29155320.

54. Malpica Castillo LE, Campuzano-Zuluaga G, Toomey NL, et al. Targeting CD30 Expression in Adult T-Cell Leukemia-Lymphoma (ATLL). Blood 2017;130:374. Available at: http://www.bloodjournal.org/content/130/Suppl_1/374.abstract.

T-Cell Prolymphocytic Leukemia

Overview

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.[1] Skin lesions can also be present in about 30% of patients, although the cutaneous presentation is not well characterized.[2,3]

Recurrent inversions or translocations involving chromosome 14, inv(14)(q11;q32) or t(14;14)(q11;q32), resulting in the overexpression of *TCL-1* oncogene are the most common cytogenetic abnormalities observed in T-PLL.[4-7] Although less frequent, the translocation t(X;14)(q28;q11), leading to overexpression of the *MTCP-1* oncogene, may also occur.[8,9] 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.[10,11] *ATM* 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.[10,11] Abnormalities in chromosome 8, mainly trisomy 8q, are also frequently observed.[4,5] More recently gene sequencing studies have identified a high frequency of mutations in genes in the *JAK-STAT* pathway that could contribute to the pathogenesis of T-PLL.[12-14] The presence of complex karyotype (≥5 cytogenetic abnormalities) has also been reported as a poor prognostic factor in patients with T-PLL.[15]

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for T-Cell Lymphomas, a literature search of the PubMed database was performed to obtain key literature in T-PLL published between May 2016 and December 2017. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[16]

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 18 citations and their potential relevance was examined. The data from key PubMed articles selected by the panel for review during the Guidelines update meeting 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 website.

Diagnosis

Morphologic examinations of peripheral blood smear, 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 typical 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.[17] 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.

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+.[17] 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.[1] CD52 is often highly expressed.[18] Peripheral blood flow cytometry analysis should include the following markers: TdT, CD1a, CD2, CD3, CD4, CD5, CD7, CD8, CD52, and TCRαβ. In general, bone marrow biopsy is not essential for establishing a diagnosis of T-PLL. Under certain circumstances, 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.

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 clonal *TCR* gene rearrangements and IHC for 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 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 CMV serology should be strongly considered prior to initiation of treatment with alemtuzumab-containing regimens.

Treatment Options

First-line Therapy

T-PLL is an aggressive malignancy associated with rapid disease progression, and in most cases of T-PLL patients are symptomatic at the time of presentation. In the minority of patients who are asymptomatic with a more indolent course of disease, observation is a reasonable approach until symptoms develop.

In an early study of 78 patients with T-PLL treated with alkylating agents, pentostatin, or CHOP, the median OS was only 7.5 months; among the subgroup of patients who responded to pentostatin (n= 15), the median OS was 16 months.[1] In a retrospective analysis of patients (both previously untreated and treated) with post-thymic T-cell malignancies treated with pentostatin, the ORR was 45% (CR rate of 9%) for patients with T-PLL (n = 55).[19] 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 disease and 9 months for non-responding disease.[19]

Treatment with the anti-CD52 monoclonal antibody alemtuzumab results in high response rates in both previously treated and untreated T-PLL.[20-23] In a study that primarily included patients with pretreated T-PLL, intravenous (IV) alemtuzumab resulted in an ORR of 76% (60% CR rate).[21] The median disease-free interval was 7 months. Among the patients with pretreated T-PLL (n = 37), none had achieved a CR to previous therapy and 61.5% were resistant to prior treatments.[21] The median OS for all patients was 10 months, and was 16 months for patients with a CR. Following alemtuzumab, 11 patients HCT (autologous HCT, n = 7; allogeneic HCT, n = 4). Similar outcomes were reported in a subsequent report, in which IV alemtuzumab induced an ORR of 74% (CR rare of 60%) in patients with relapsed/refractory T-PLL (n = 45); the 4-year OS rate in this patient group was 18%.[23] 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 rate of 39.5%); among the 4 patients who received alemtuzumab as first-line therapy, 3 achieved a CR.[22] The 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.[22] The most common toxicities reported with alemtuzumab in patients with T-PLL included infusion-related reactions, prolonged lymphocytopenia, and infectious events, including opportunistic infections.[21,22]

Alemtuzumab has also been evaluated as part of combination regimens in patients with T-PLL. A prospective multicenter phase II study conducted by the German CLL Study Group evaluated the safety and efficacy of induction chemotherapy with FCM (fludarabine, cyclophosphamide, mitoxantrone) followed by consolidation with alemtuzumab in patients who were previously treated (n = 9) and treatment-naive (n = 16). Patients with SD or progression after 2 courses of FCM were also eligible to received alemtuzumab.[24] Following FCM chemotherapy, 21 patients subsequently received consolidation with IV alemtuzumab. The ORR after FCM was 68% with a CR rate of 24%. After consolidation with alemtuzumab, the ORR increased to 92% with a CR rate of 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%). 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 infectious complications.

In a phase II study that evaluated the combination of alemtuzumab and pentostatin in patients with T-cell malignancies, this regimen resulted in an ORR of 69% (CR rate of 62%) in the subgroup of patients with T-PLL (n = 13). The median PFS and OS for this subgroup of patients were 8 months and 10 months, respectively.[25] The study included both patients with previously treated and untreated disease. In a more recent study that analyzed the characteristics and clinical outcome of 119 patients with T-PLL, 55 patients with previously untreated T-PLL received treatment with an alemtuzumab-based regimen (42 patients received alemtuzumab monotherapy and 13 patients received alemtuzumab combination with pentostatin).[26] The ORR and CR rate for alemtuzumab monotherapy were 83% and 66%, respectively. The corresponding response rates were 82% and 73% respectively, for alemtuzumab in combination with

pentostatin. In this study, the presence of pleural effusion, high LDH, and low hemoglobin were associated with shorter OS.

Hematopoietic Cell Transplant

The potential utility of HCT in patients with T-PLL has been reported in a number of individual case studies and retrospective analyses.[27-34]

A retrospective study reviewed the outcomes of 28 patients with T-PLL treated with either allogeneic (n = 13) or autologous HCT (n = 15) after alemtuzumab.[31] The clinical outcomes were compared against a retrospective cohort of 23 patients with T-PLL who achieved a CR and survived >6 months after alemtuzumab but did not undergo HCT. Among the 13 patients who received allogeneic HCT after alemtuzumab (9 patients had a CR and 4 patients had a PR at the time of transplant), all patients achieved a CR following allogeneic HCT (except one patient who was not evaluable), and 5 were alive with a CR after a median follow-up of 28 months after transplant.[31] The median OS for all patients who underwent allogeneic HCT was 33 months, which was more favorable compared to the median OS of 20 months for the retrospective cohort of patients treated with alemtuzumab alone. However, allogeneic HCT was associated with a TRM rate of 31%. Among the 15 patients who received autologous HCT after alemtuzumab (11 patients had a first CR, 2 patients had a second CR, and 2 patients had a PR at the time of transplant), all of the 15 patients achieved a CR following autologous HCT and 5 patients were alive with a CR at 8, 45, 81, 107, and 115 months after transplant. Nine patients had relapsed at a median of 15 months from transplant, and all died. The median OS (from start of alemtuzumab therapy) for all patients who underwent autologous HCT was 52 months, which appeared to compare favorably to that of a retrospective cohort of patients who received alemtuzumab alone (20 months). No statistically significant difference in OS was observed between autologous versus allogeneic HCT (52 months vs. 33 months).

In a review of data from the CIBMTR database (47 patients with PLL treated with allogeneic HCT), the 1-year PFS and OS rates were 33% and 48%, respectively.[32] The median OS was 11 months. For the subgroup of patients with T-PLL (n = 21), the median PFS with allogeneic HCT was 5 months. The 1-year cumulative incidence of TRM and the incidence of relapse or disease progression were 28% and 39%, respectively.[32] In another study that evaluated the outcome of allogeneic HCT in 41 patients with T-PLL from the EBMT database, the median PFS, OS, and 3-year RFS and OS rates were 10 months, 12 months, 19%, and 21%, respectively.[33] The 3-year TRM and relapse rates were 41% for both endpoints; most relapses (71% of cases) occurred within the first year following transplant.[33] Patients who underwent HCT in first remission (CR or PR) tended to have a lower relapse rate (2-year rate: 30% vs. 46%) and higher EFS 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 HCT. None of the variables evaluated were independent predictors of OS outcomes.[33]

A more recent retrospective study reported the outcomes of allogeneic HCT in 27 patients with T-PLL identified in the registry for French Society for stem cell transplantation.[34] The majority of these patients (85%) had received alemtuzumab prior to HCT (14 patients had a CR and 10 patients had a PR). Following HCT, 21 patients achieved a CR as the best response (CR rate of 78% after HCT). After a median follow-up of 33 months, 10 patients were still alive with a continuous 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 OS and PFS rates were 36% and 26%, respectively. The relapse incidence after HCT was 47% occurring at a median of 12 months and the overall cumulative incidence of TRM at 3 years was 31%.

These data from retrospective studies suggest that allogeneic HCT may offer the best chance for long-term disease control in a subgroup of patients with 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. Monotherapy with IV alemtuzumab is the preferred primary treatment option for patients with symptomatic disease.[23] Sequential therapy with FCM followed by IV alemtuzumab[24] or pentostatin in combination with alemtuzumab[25,26] are included as alternate treatment options for selected patients with bulky disease, splenomegaly, and hepatic involvement who may not respond well to alemtuzumab monotherapy. In the minority of patients who are asymptomatic with a more indolent course of disease, observation is a reasonable approach until symptoms develop.

SC alemtuzumab is associated with inferior response rates and survival than IV alemtuzumab.[23,35] In the small number of patients who were treated with SC alemtuzumab (n = 9), the ORR was 33% with no CR rate; moreover, 2 of the patients (22%) died of progression of disease during therapy. In contrast, IV alemtuzumab (n = 32) induced an ORR of 91% with a CR in 81% of patients. In a retrospective analysis that included 41 patients with T-PLL, there was a significant survival difference among patients treated with IV and SC alemtuzumab (41 months vs.14 months; $P = .0014$).[35] Based on these data showing inferior response rates with the SC alemtuzumab, the panel recommends the use of IV alemtuzumab.

Given the potential risks for viral reactivation and opportunistic infections associated with alemtuzumab, routine monitoring for CMV reactivation and the use of anti-infective prophylaxis for herpes virus and *Pneumocystis jiroveci* pneumonia (PCP) is recommended for all patients receiving alemtuzumab-based regimens. See *Supportive Care: Monoclonal Antibody Therapy and Viral Reactivation* in the algorithm.

In patients who achieve a CR or PR following initial therapy, consolidation with allogeneic HCT should be considered.[31-34] Autologous HCT may be considered, if a donor is not available and if the patient is not physically fit enough to undergo allogeneic HCT.[31]

Disease relapse following an initial response to therapy, disease not responding to initial therapy, or disease progression during initial therapy should be managed with alternate regimens not used during first-line therapy. At this time, the limited availability of data precludes any definitive recommendations for the management of relapsed/refractory disease.[36-38]

References

1. Matutes E, Brito-Babapulle V, Swansbury J, et al. Clinical and laboratory features of 78 cases of T-prolymphocytic leukemia. Blood 1991;78:3269-3274. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1742486.

2. Magro CM, Morrison CD, Heerema N, et al. T-cell prolymphocytic leukemia: an aggressive T cell malignancy with frequent cutaneous tropism. J Am Acad Dermatol 2006;55:467-477. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16908353.

3. Hsi AC, Robirds DH, Luo J, et al. T-cell prolymphocytic leukemia frequently shows cutaneous involvement and is associated with gains of MYC, loss of ATM, and TCL1A rearrangement. Am J Surg Pathol 2014;38:1468-1483. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25310835.

4. Brito-Babapulle V, Catovsky D. Inversions and tandem translocations involving chromosome 14q11 and 14q32 in T-prolymphocytic leukemia and T-cell leukemias in patients with ataxia telangiectasia. Cancer Genet Cytogenet 1991;55:1-9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1913594.

5. Maljaei SH, Brito-Babapulle V, Hiorns LR, Catovsky D. Abnormalities of chromosomes 8, 11, 14, and X in T-prolymphocytic leukemia studied by fluorescence in situ hybridization. Cancer Genet Cytogenet 1998;103:110-116. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9614908.

6. Virgilio L, Lazzeri C, Bichi R, et al. Deregulated expression of TCL1 causes T cell leukemia in mice. Proc Natl Acad Sci U S A 1998;95:3885-3889. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9520462.

7. Herling M, Patel KA, Teitell MA, et al. High TCL1 expression and intact T-cell receptor signaling define a hyperproliferative subset of T-cell prolymphocytic leukemia. Blood 2008;111:328-337. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17890451.

8. Stern MH, Soulier J, Rosenzwajg M, et al. MTCP-1: a novel gene on the human chromosome Xq28 translocated to the T cell receptor alpha/delta locus in mature T cell proliferations. Oncogene 1993;8:2475-2483. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8361760.

9. de Oliveira FM, Tone LG, Simoes BP, et al. Translocations t(X;14)(q28;q11) and t(Y;14)(q12;q11) in T-cell prolymphocytic leukemia. Int J Lab Hematol 2009;31:453-456. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18294235.

10. Stilgenbauer S, Schaffner C, Litterst A, et al. Biallelic mutations in the ATM gene in T-prolymphocytic leukemia. Nat Med 1997;3:1155-1159. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9334731.

11. Stoppa-Lyonnet D, Soulier J, Lauge A, et al. Inactivation of the ATM gene in T-cell prolymphocytic leukemias. Blood 1998;91:3920-3926. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9573030.

12. Bergmann AK, Schneppenheim S, Seifert M, et al. Recurrent mutation of JAK3 in T-cell prolymphocytic leukemia. Genes Chromosomes Cancer 2014;53:309-316. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24446122.

13. Kiel MJ, Velusamy T, Rolland D, et al. Integrated genomic sequencing reveals mutational landscape of T-cell prolymphocytic leukemia. Blood 2014;124:1460-1472. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24825865.

14. Lopez C, Bergmann AK, Paul U, et al. Genes encoding members of the JAK-STAT pathway or epigenetic regulators are recurrently mutated in T-cell prolymphocytic leukaemia. Br J Haematol 2016;173:265-273. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26917488.

15. Hu Z, Medeiros LJ, Fang L, et al. Prognostic significance of cytogenetic abnormalities in T-cell prolymphocytic leukemia. Am J Hematol 2017;92:441-447. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28194886.

16. U.S. National Library of Medicine Key MEDLINE® Indicators Available at: http://www.nlm.nih.gov/bsd/bsd_key.html.

17. Catovsky D, Muller-Hermelink HK, Ralfkiaer E, eds. T-cell prolymphocytic leukaemia. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO Classification of Tumours or Haematopoietic and Lymphoid Tissues (ed 4th). Lyon2008.

18. Ginaldi L, De Martinis M, Matutes E, et al. Levels of expression of CD52 in normal and leukemic B and T cells: correlation with in vivo therapeutic responses to Campath-1H. Leuk Res 1998;22:185-191. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9593475.

19. Mercieca J, Matutes E, Dearden C, et al. The role of pentostatin in the treatment of T-cell malignancies: analysis of response rate in 145 patients according to disease subtype. J Clin Oncol 1994;12:2588-2593. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7989933.

20. Pawson R, Dyer MJ, Barge R, et al. Treatment of T-cell prolymphocytic leukemia with human CD52 antibody. J Clin Oncol 1997;15:2667-2672. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9215839.

21. Dearden CE, Matutes E, Cazin B, et al. High remission rate in T-cell prolymphocytic leukemia with CAMPATH-1H. Blood 2001;98:1721-1726. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11535503.

22. Keating MJ, Cazin B, Coutre S, et al. Campath-1H treatment of T-cell prolymphocytic leukemia in patients for whom at least one prior chemotherapy regimen has failed. J Clin Oncol 2002;20:205-213. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11773171.

23. Dearden CE, Khot A, Else M, et al. Alemtuzumab therapy in T-cell prolymphocytic leukaemia: comparing efficacy in a series treated intravenously and a study piloting the subcutaneous route. Blood 2011;118:5799-5802. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21948296.

24. Hopfinger G, Busch R, Pflug N, et al. Sequential chemoimmunotherapy of fludarabine, mitoxantrone, and cyclophosphamide induction followed by alemtuzumab consolidation is effective in T-cell prolymphocytic leukemia. Cancer 2013;119:2258-2267. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23512246.

25. Ravandi F, Aribi A, O'Brien S, et al. Phase II study of alemtuzumab in combination with pentostatin in patients with T-cell neoplasms. J Clin Oncol 2009;27:5425-5430. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19805674.

26. Jain P, Aoki E, Keating M, et al. Characteristics, outcomes, prognostic factors and treatment of patients with T-cell prolymphocytic leukemia (T-PLL). Ann Oncol 2017;28:1554-1559. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28379307.

27. Collins RH, Pineiro LA, Agura ED, Fay JW. Treatment of T prolymphocytic leukemia with allogeneic bone marrow transplantation. Bone Marrow Transplant 1998;21:627-628. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9580345.

28. Garderet L, Bittencourt H, Kaliski A, et al. Treatment of T-prolymphocytic leukemia with nonmyeloablative allogeneic stem cell transplantation. Eur J Haematol 2001;66:137-139. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11168523.

29. Murase K, Matsunaga T, Sato T, et al. Allogeneic bone marrow transplantation in a patient with T-prolymphocytic leukemia with small-intestinal involvement. Int J Clin Oncol 2003;8:391-394. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14663643.

30. de Lavallade H, Faucher C, Furst S, et al. Allogeneic stem cell transplantation after reduced-intensity conditioning in a patient with T-cell prolymphocytic leukemia: graft-versus-tumor effect and long-term remission. Bone Marrow Transplant 2006;37:709-710. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16474410.

31. Krishnan B, Else M, Tjonnfjord GE, et al. Stem cell transplantation after alemtuzumab in T-cell prolymphocytic leukaemia results in longer survival than after alemtuzumab alone: a multicentre retrospective study. Br J Haematol 2010;149:907-910. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20201944.

32. Kalaycio ME, Kukreja M, Woolfrey AE, et al. Allogeneic hematopoietic cell transplant for prolymphocytic leukemia. Biol Blood Marrow Transplant 2010;16:543-547. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19961946.

33. Wiktor-Jedrzejczak W, Dearden C, de Wreede L, et al. Hematopoietic stem cell transplantation in T-prolymphocytic leukemia: a retrospective study from the European Group for Blood and Marrow Transplantation and the Royal Marsden Consortium. Leukemia 2011;26:972-976. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22116553.

34. Guillaume T, Beguin Y, Tabrizi R, et al. Allogeneic hematopoietic stem cell transplantation for T-prolymphocytic leukemia: a report from the French society for stem cell transplantation (SFGM-TC). Eur J Haematol 2015;94:265-269. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25130897.

35. Damlaj M, Sulai NH, Oliveira JL, et al. Impact of Alemtuzumab Therapy and Route of Administration in T-Prolymphocytic Leukemia: A Single-Center Experience. Clin Lymphoma Myeloma Leuk 2015;15:699-704. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26422251.

36. Herbaux C, Genet P, Bouabdallah K, et al. Bendamustine is effective in T-cell prolymphocytic leukaemia. Br J Haematol 2015;168:916-919. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25316212.

37. Hasanali ZS, Saroya BS, Stuart A, et al. Epigenetic therapy overcomes treatment resistance in T cell prolymphocytic leukemia. Sci Transl Med 2015;7:293ra102. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26109102.

38. Boidol B, Kornauth C, van der Kouwe E, et al. First-in-human response of BCL-2 inhibitor venetoclax in T-cell prolymphocytic leukemia. Blood 2017;130:2499-2503. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28972014.

Extranodal NK/T-Cell Lymphomas, Nasal Type

Overview

NK/T-cell lymphomas are a rare and distinct subtype NHL.[1] NK/T-cell lymphomas are predominantly extranodal and the majority of these are of nasal type, often localized to the upper aerodigestive tract including the nasal cavity, nasopharynx, paranasal sinuses, tonsils, hypopharynx, and larynx.[2,3] The most common clinical features of extranodal NK/T-Cell lymphomas (ENKL), nasal type include nasal obstruction or nasal bleeding.[2,3] However, ENKL can have an extranasal presentation, with skin, testis, and gastrointestinal tract being the most common sites of extranasal involvement or metastatic disease.[2,4,5]

In an analysis of 1153 patients with a confirmed diagnosis of T-cell or NK-cell lymphomas from the International T-cell Lymphoma Project, 136 patients (12%) had ENKL (nasal 68%, extranasal 26%, aggressive or unclassifiable 6%) and the frequency was higher in Asia than in Western countries (22% vs. 5%).[4] A greater proportion of the patients with extranasal disease present with advanced-stage disease (68% vs. 27%), mass >5 cm (68% vs. 12%), >2 extranodal sites (55% vs. 16%), elevated LDH levels (60% vs. 45%), and B symptoms (54% vs. 39%) than those with ENKL, nasal type.[4] The median OS and failure-free survival (FFS) for the entire cohort were only 8 months and 6 months, respectively. ENKL, nasal type was associated with longer median OS (19 months vs. 4 months) and higher 5-year OS rate (42% vs. 9%).

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for T-Cell Lymphomas, a literature search of the PubMed database was performed to obtain key literature in ENKL published between May 2016 and September 2017. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[6]

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 literature search resulted in 123 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 website.

Diagnosis

Histopathologic 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.[2] 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 for the evaluation of occult disease even in areas that are not clearly involved on endoscopic examination.

Adequate immunophenotyping is essential to confirm the diagnosis. The initial IHC panel should include cytoplasmic CD3ε (cCD3ε), CD56. Additional recommended markers for the IHC panel include CD20 for B-cell lineage; CD2, CD4, CD5, CD7, and CD8 for T-cell lineage; CD30; and Ki-67. EBV infection is always present in ENKL and should be determined by EBV-encoded RNA in situ hybridization (EBER-ISH). A negative EBER-ISH result should prompt hematopathology review for an alternative diagnosis. Clonal T-cell receptor (*TCR*) gene rearrangements have been found in up to a third of cases with ENKL, nasal type.[4] Molecular analysis to detect clonal *TCR* gene rearrangements may be useful under certain circumstances.

The typical immunophenotype for NK-cell ENKL is CD20-, CD2+, cCD3ε+ (surface CD3-), CD4-, CD5-, CD7-/+, CD8-/+, CD43+, CD45RO+, CD56+, TCRαβ-, TCRδγ-, EBV-EBER+, and cytotoxic granule proteins positive (eg, TIA-1+, granzyme B+).[4,7] 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.[8,9] High Ki-67 expression (65% or more) was associated with a shorter OS and DFS. In multivariate analysis, Ki-67 expression and primary site of involvement were found to be independent prognostic factors for both OS and DFS.[8]

Workup

The initial workup should include a history and physical examination with attention to node-bearing areas (including Waldeyer's ring), testicles and skin, complete ENT evaluation of nasopharynx, as well as evaluation of B-symptoms and performance status. Laboratory tests should include a CBC with differential, comprehensive metabolic panel, measurement of serum uric acid, and LDH. CT scans of chest, abdomen, and pelvis, with contrast of diagnostic quality and/or PET/CT should be performed. 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. Bone marrow biopsy and aspirate is recommended. Bone marrow involvement is uncommon at diagnosis and occurs in less than 10% of patients.[10] Morphologically negative biopsies should be evaluated by EBER-ISH and, if positive, should be considered involved.[10-13]

Measurement of EBV-DNA viral load by quantitative PCR is useful in the diagnosis and often in the monitoring of the disease. EB- DNA viral load correlates well with clinical stage, response to therapy, and survival.[14,15] EBV-DNA ≥6.1×10^7 copies/mL at presentation has been shown to be associated with an inferior DFS.[14] Pretreatment EBV-DNA level in whole blood and plasma has been shown to be a good predictor of response and survival after treatment with asparaginase-based chemotherapy in patients with ENKL, nasal type.[16-19] In the phase II study from the NK-Cell Tumor Study Group, the ORR was significantly higher in patients with $<10^5$ copies/mL of EBV-DNA in whole blood prior to initiation of asparaginase-based chemotherapy (90% vs. 20%, $P = .007$) and in patients with $<10^4$ copies/mL of EBV-DNA in plasma (95% vs. 29%, $P = .002$).[18] In addition, the incidence of grade 4 non-hematologic toxicity was significantly higher among patients with ≥10^5 copies/mL of EBV-DNA in whole blood (100% vs. 29%, $P = .007$) and in patients with ≥10^4 copies/mL of EBV-DNA in plasma (86% vs. 26%, $P = .002$).

The use of IPI, most commonly used for patients with aggressive lymphomas, is limited in patients with ENKL because most patients present with localized disease, rare involvement of bone marrow, and the presence of constitutional symptoms even with localized disease. Lee et al have proposed a prognostic model specifically for patients with ENKL, nasal type, that stratifies patients into 4 risk groups (low risk, low-intermediate risk, intermediate-high risk, and high risk) 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).[20] Most patients had received anthracycline-based chemotherapy regimens with or without RT. Kim et al have proposed a prognostic index of natural killer lymphoma (PINK) for ENKL treated with non-anthracycline-based chemotherapy.[21] In a retrospective analysis of 527 patients, age >60 years, stage III or IV disease, distant lymph-node involvement and non-nasal type disease were identified as predictors of OS and PFS. Among the 328 patients with data for EBV-DNA, detectable EBV-DNA measured by quantitative PCR was a significant predictor of OS. Based on these risk factors, PINK stratified patients into 3 risk groups (low-risk, no risk factors; intermediate-risk, one risk factor; and high-risk, ≥2 risk factors) with 3-year OS rates of 81%, 62%, and 25%, respectively. PINK-E (for patients with data for EBV-DNA) also stratified patients into 3 risk groups (low-risk; 0 or 1 risk factor, intermediate-risk; 2 risk factors and high-risk; ≥3 risk factors) with 3-year OS rates of 81%, 55%, and 28%, respectively.

The NCCN Guidelines recommend measurement of EBV-DNA load and calculation prognostic index (PINK or PINK-E) as part of initial workup.

Treatment Options

Radiation Therapy With or Without Chemotherapy

RT is an important component of initial treatment and RT alone has also been effective in achieving favorable CR rates compared to chemotherapy alone in patients with localized ENKL.[4,22-28]

In the analysis of the International T-cell Lymphoma Project, which retrospectively reviewed the clinical outcome of 136 patients with ENKL, more patients with ENKL, nasal type received RT with or without anthracycline-based chemotherapy compared with patients with extranasal ENKL (52% vs. 24%); the remainder of patients received chemotherapy alone.[4] 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%; P = .045).[4]

In a retrospective review of 105 patients with localized stage I/II ENKL, nasal type, RT alone resulted in higher CR rates than with chemotherapy alone (83% vs. 20%); CR rates improved to 81% among patients who received RT following chemotherapy.[24] 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, in this study, the addition of chemotherapy to RT did not appear to improve OS outcomes.[24]

Early or up-front RT at doses of ≥54 Gy (alone or in combination with chemotherapy) was associated with better survival outcomes in patients with localized ENKL, nasal type in the upper aerodigestive tract.[25] Among 74 patients who received RT as a component of initial therapy, the 5-year OS and DFS rates were 76% and 60%, respectively, for patients treated with RT doses of ≥54 Gy, compared with 46% and

33%, respectively, for patients treated with RT doses of <54 Gy. Among patients with stage I disease, up-front RT was associated with higher survival rates than early RT following initial chemotherapy (5-year OS rates were 90% vs. 49%, *P* = .012; 5-year DFS rates were 79% vs. 40%, *P* = .021).

RT following chemotherapy also resulted in significantly higher response rates and prolonged survival in patients with advanced stage disease.[27] In a retrospective analysis of 73 patients with stage III-IV disease, the ORR was significantly higher in patients treated with chemotherapy followed by RT than those treated with chemotherapy alone (82% vs. 29%; *P* < .001). The 2-year OS rates were 58% versus 15%, (*P* < .001) and the 2-year PFS rates were 46% versus 8%, (*P* < .001). RT significantly improved the prognosis of patients who achieved a CR or PR after initial chemotherapy (2-year OS rates were 82% vs. 40%, *P* = .002; 2-year PFS rates were 66% vs. 23%, *P* = .008) but failed to provide a significant survival advantage among those with stable or PD after initial chemotherapy.

Concurrent Chemoradiation

Concurrent chemoradiation (with or without consolidation chemotherapy) is a feasible and effective treatment for localized ENKL. 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 chemoradiation (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 of 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). The results of a more recent retrospective analysis (358 patients; 257 patients had localized disease) also reported favorable response and survival rates for patients treated with concurrent RT-DeVIC regimen.[31] After a median follow-up of 5.6 years, the 5-year OS and PFS rates were 72% and 61%, respectively. In this analysis, only 4% of patients with localized disease were classified as high risk according to PINK. In multivariate analysis, elevated soluble interleukin-2 receptor was an independent predictive factor for worse OS and PFS among patients treated with RT-DeVIC.

Another phase II study also reported promising results with concurrent chemoradiation (cisplatin and 40–52.8 Gy RT) followed by 3 cycles of etoposide, ifosfamide, cisplatin, and dexamethasone (VIPD) in patients with ENKL, nasal type (n = 30; 21 patients had stage I/II disease and 9 patients had stage III/IV disease).[32] 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.[32] The safety and efficacy of concurrent chemoradiation followed by consolidation chemotherapy in patients with localized ENKL, nasal type has also been confirmed in more recent studies.[33,34]

Asparaginase-based or Pegaspargase-based Chemotherapy or Chemoradiation

ENKL 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 chemotherapy.[35] Asparaginase-based or pegaspargase-based regimens have been evaluated to improve response rates.

The SMILE regimen (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) has been evaluated in patients with

newly diagnosed and relapsed/refractory ENKL, nasal type.[36,37] A phase II study from the NK-Cell Tumor Study Group evaluated the safety and efficacy of the SMILE regimen in patients with newly diagnosed stage IV, and relapsed or refractory ENKL, nasal type (n = 38). 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.[36] 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.[36] Another phase II study from the Asia Lymphoma Study Group (n = 87) also reported favorable outcomes with the SMILE regimen in patients with newly diagnosed or relapsed/refractory ENKL, nasal type.[37] 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%.

The modified SMILE regimen (a single dose of pegaspargase is substituted for 7 doses of L-asparaginase per cycle) was also shown to be active for the treatment of ENKL.[38,39] In a retrospective analysis of 43 patients with ENKL, nasal type was treated at a single institution (26 patients with early-stage disease received 2 cycles of chemotherapy followed by 45 Gy ISRT; 17 patients with advanced-stage disease received 3 cycles of chemotherapy alone and ISRT to bulky disease sites).The modified SMILE regimen resulted in a significantly higher CR rate than the accelerated-CHOP regimen (80% vs. 30%; $P = .015$), and the 2-year OS (87% vs. 21%) and PFS (56% vs.18%) rates were significantly higher for patients with early stage disease than advanced-stage disease ($P < .001$) for the total cohort of patients.[39] Among 11 patients with early-stage disease treated with the modified SMILE regimen and 45 Gy of ISRT, the estimated 2-year PFS rate was 83% and all patients were alive with no evidence of disease at the time of publication.

Pegaspargase in combination with gemcitabine and oxaliplatin (P-GEMOX) with or without RT is also an effective treatment option for newly diagnosed as well as relapsed/refractory disease.[40,41] In a retrospective analysis of 117 patients with ENKTL (96 patients with newly diagnosed ENKL and 21 patients with relapsed/refractory disease), the P-GEMOX regimen resulted in an ORR of 88% and responses were similar for patients with newly diagnosed and relapsed/refractory ENKL.[40] After a median follow-up of 17 months, the 3-year OS and PFS rates were 73% and 58%, respectively. In a subgroup analysis, PFS was significantly better for patients with newly diagnosed ENKL than relapsed/refractory disease, but there were no differences in OS. AspaMetDex regimen (L-asparaginase, methotrexate and dexamethasone) was evaluated in a phase II intergroup study in 19 patients with refractory or relapsed ENKL.[16] 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 rates after 3 cycles of AspaMetDex were 78% and 61%, respectively. The median PFS and OS were both 1 year; the absence of anti-asparaginase antibodies and the disappearance of serum EBV-DNA were significantly associated with a better outcome.[16]

Sandwich chemoradiation (2 cycles of chemotherapy followed by IFRT [56 Gy] followed by 2–4 cycles of chemotherapy within 7 days of completion of IFRT) with asparaginase-based or pegaspargase-based chemotherapy has been shown to be effective for the treatment of newly diagnosed stage I-II ENKL, nasal type.[42-44] In a phase II study of 27 patients with newly diagnosed stage I-II ENKL, nasal type, sandwich chemoradiation with GELOX regimen (L-asparaginase, gemcitabine,

and oxaliplatin) resulted in an ORR of 96% (CR in 74%). After a median follow-up of 63 months, the 5-year OS and PFS rates were 85% and 74%, respectively. Grade 3 or 4 toxicities were infrequent, and no treatment-related deaths were reported.[42] In another phase II study of 26 patients with newly diagnosed stage I-II ENKL, nasal type, sandwich chemoradiation with LVP regimen (L-asparaginase, vincristine, and prednisone; 2 or 3 cycles) resulted in an ORR of 89% (CR in 81%). After a median follow-up of 67 months, the 5-year PFS and OS rates were both 64%.[43] In a subgroup analysis, the 5-year OS rates were higher for patients who achieved a CR (76% compared to 0% for those without a CR). Grade 3 leukocytopenia occurred in 2 patients (8%), and no grade 4 toxicities or treatment-related deaths were reported. Sandwich chemoradiation with the P-GEMOX regimen is also effective for the treatment of patients with newly diagnosed ENKL (n = 38) resulting in an ORR of 92% (87% CR). At a median follow-up of 15.5 months, the 1-year PFS and OS were both 87%.[44] Long-term benefit of this approach needs to be confirmed in larger prospective randomized clinical trials.

RT is also an independent prognostic factor for OS and PFS in ENKL in patients with stage I-II ENKL treated with asparaginase-based chemotherapy.[45] In a retrospective analysis of 143 patients with stage I-II ENKL treated with asparaginase-based chemotherapy with or without RT, the 2-year OS rates (90% vs. 49%; $P < .001$) and PFS rates (87% vs. 37%; $P < .001$) were significantly higher for patients who received RT. The survival benefit was also seen in patients who achieved CR after chemotherapy. The 2-year OS and PFS rates were 91% and 86% for patients treated with RT, compared to 60% (both OS and PFS) for those who did not receive RT.

Hematopoietic Cell Transplant

Autologous HCT has been evaluated as a consolidation therapy for patients with early- and advanced-stage ENKL responding to primary therapy. In retrospective analyses, disease status at the time of transplant was the most important prognostic factor for OS and RFS.[46-49] A retrospective analysis of 47 patients that evaluated the survival benefits of autologous HCT showed that among patients with CR at the time of transplant, the 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).[48] 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 non-transplant control groups for patients with low risk (87% vs. 69%), whereas the survival benefit with transplant was significantly greater (100% vs. 52%) for patients in the high-risk group.[48] In a retrospective analysis of 62 patients with newly diagnosed ENKL who underwent autologous HCT after primary therapy, patients with early-stage disease had significantly better 3-year PFS (64% vs. 40%, $P = .017$) and OS (68% vs. 52%, $P = .048$) than those with advanced disease.[49] In the multivariate analysis, NK/T-cell prognostic index (for limited disease) and pretransplant response (for advanced-stage disease) were independent prognostic factors for survival. In addition, RT was an independent prognostic factor for reduced progression and survival in patients with limited disease, and anthracycline-based chemotherapy was a poor prognostic factor for progression in patients with advanced disease. In a more recent report, pre-transplant response status assessed by Deauville 5-PS and the presence of detectable EBV-DNA were identified as independent predictors of OS following autologous HCT.[50]

Allogeneic HCT has also been evaluated in retrospective studies predominantly in Asian patients.[47,51,52] In a retrospective, questionnaire-based study that included 22 patients with ENKL who underwent allogeneic HCT with primarily myeloablative regimens, the 2-year PFS and OS rates were 34% and 40%, respectively.[51] In another retrospective analysis that evaluated the role of allogeneic HCT in 18 patients with stage IV ENKL at first CR or chemotherapy-sensitive relapsed/refractory disease, the 5-year OS and EFS rates were 57% and 51%, respectively.[52] The use of the SMILE regimen prior to HCT was the most important positive prognostic indicator for superior OS and EFS ($P < .01$). In a more recent retrospective analysis from CIBMTR that evaluated the allogeneic HCT in a predominantly Caucasian patient cohort, the 3-year PFS and OS rates were 28% and 34% respectively.[53] The survival rates were similar regardless of the remission status prior to allogeneic HCT suggesting that allogeneic HCT may be associated with a survival benefit even in the subset of patients with chemorefractory disease at the time of transplant. Several small case reports have also reported favorable long-term outcomes after allogeneic HCT in patients with relapsed/refractory ENKL.[54-56]

In a 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) and allogeneic (n = 74) HCT in patients with ENKL.[57] A greater proportion of patients had stage IV disease in the allogeneic HCT group compared with the autologous HCT group (64% vs. 33%), and a smaller proportion in the allogeneic HCT group had low-risk IPI scores (34% vs. 62%). Thus, patients who underwent autologous HCT in this series appeared to have better prognostic features. The 2-year OS rate was significantly higher with autologous HCT compared with allogeneic HCT (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 (ie, stage IV disease, non-CR and performance status at transplant).[57]

NCCN Recommendations

Participation in a clinical trial is the preferred option for all patients with ENKL with any stage of disease. It is recommended that patients with ENKL be treated at centers with expertise in the management of this disease and, when possible, enrolled in clinical trials. Because ENKL are rare malignancies, randomized trials comparing different regimens have not been conducted to date. Most of the available data are from retrospective analyses and small prospective series. Therefore, standard therapy has not yet been established for patients with ENKL. Retrospective comparative studies have shown that asparaginase-based or pegaspargase-based regimens are associated with superior efficacy than the conventional anthracycline-based regimens for the treatment of stage I-II disease.[58,59] 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.

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 or II nasal disease are further stratified based on their performance status and ability to tolerate chemotherapy.

RT alone is recommended for patients with stage I or II nasal disease who are unfit to receive chemotherapy. Patients with stage I or II nasal disease who are fit to receive chemotherapy can be treated with concurrent chemoradiation [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 [modified SMILE followed by RT (45–50.4 Gy)] or sandwich chemoradiation (2 cycles of P-GEMOX followed by RT 56 Gy followed by 2–4 cycles of P-GEMOX).

ISRT is recommended as the appropriate field as it limits the volume of RT to the region of involvement only.[60] An ISRT dose of 50 to 55 Gy is recommended when used alone as primary treatment and 45 to 50.4 Gy is recommended when used in combination with chemotherapy. When ISRT is used alone, the CTV should encompass the involved region as defined by MRI and CT scan, with expansions to include any of the sinuses that were initially partially involved, all adjacent paranasal sinuses, as well as a 0.5 to 1 cm expansion into soft tissue.[60] In instances when chemotherapy was given prior to ISRT and has produced a CR, the CTV should include at least the prechemotherapy GTV with appropriate margins (0.5–1 cm). Recommendations for planning and treatment with ISRT are outlined in the *Principles of Radiation Therapy* section of the algorithm.

Patients with stage IV nasal disease and patients with extranasal disease (stage I-IV) can be treated with pegaspargase-based combination chemotherapy (AspaMetDex, modified SMILE or P-GEMOX regimen) with or without RT, or concurrent chemoradiation [RT (50 Gy) and 3 courses of DeVIC or concurrent RT(40–52.8 Gy) and cisplatin followed by 3 cycles of VIPD]. Pegaspargase-based combination chemotherapy alone may be appropriate for selected patients who are not eligible to receive RT. The P-GEMOX regimen is an option for patients who cannot tolerate intense chemotherapy.

Response Assessment and Additional Therapy

End-of-treatment evaluation after induction therapy should include appropriate imaging studies (CT, MRI, or PET/CT) based on the type of imaging performed at the initial workup, endoscopy with visual inspection, repeat biopsies, and measurement of EBV DNA. Recent reports from retrospective studies suggest that post-treatment PET/CT using the Deauville 5PS may be a valuable tool for response assessment in patients with newly diagnosed and relapsed/refractory disease.[61-63] In a retrospective analysis of 102 patients with newly diagnosed ENKL, Deauville 5PS and EBV DNA after completion of initial treatment were independently associated with PFS and OS in the multivariable analysis.[62] Given the primarily extranodal sites of involvement often outside of the chest, abdomen, and pelvis, PET/CT is also preferred for follow-up to better assess these sites.

Patients with stage I or II nasal disease achieving a CR to induction therapy may be observed without further treatment. A CR should also include a negative ENT evaluation. Biopsy is recommended for patients with a PR after induction therapy and those with a negative biopsy may be observed without further treatment. Patients with a positive biopsy should be managed as described below for refractory disease.

Patients with stage IV nasal disease or extranasal disease (stage I-IV) achieving a CR to induction therapy should be considered for HCT. There are no clear data to suggest whether allogeneic or autologous HCT is preferred and treatment should be individualized.[57] Biopsy is recommended for patients with a PR after induction therapy and those with a negative biopsy should be considered for HCT. Patients with a positive biopsy should be managed as described below for refractory disease.

Relapsed/Refractory Disease

Second-line therapy with pegaspargase-based combination chemotherapy, as described for induction therapy, may offer benefit for patients with refractory disease (nasal or extranasal, and regardless of

disease stage). Clinical trial or best supportive care are also included as options for refractory disease with no response to induction therapy.

Clinical trial is the preferred treatment option for relapsed/refractory disease following treatment with pegaspargase-based regimens. Pembrolizumab, anti-programmed death 1 antibody has been shown to induce high response rates in patients with relapsed/refractory ENKL following treatment with asparaginase-based regimens.[64] Pembrolizumab is an appropriate option in the absence of a clinical trial. Only limited data exist regarding the role of HCT in this patient population. Allogeneic HCT is preferred, if a donor available.

References

1. Teras LR, DeSantis CE, Cerhan JR, et al. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. CA Cancer J Clin 2016;66:443-459. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27618563.

2. Chan JKC, Quintanilla-Martinez L, Ferry JA, Peh S-C. Extranodal NK/T-cell lymphoma, nasal type. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:285-288.

3. Liang R. Advances in the management and monitoring of extranodal NK/T-cell lymphoma, nasal type. Br J Haematol 2009;147:13-21. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19604234.

4. Au W-y, Weisenburger DD, Intragumtornchai T, et al. Clinical differences between nasal and extranasal natural killer/T-cell lymphoma: a study of 136 cases from the International Peripheral T-Cell Lymphoma Project. Blood 2009;113:3931-3937. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19029440.

5. Kim SJ, Jung HA, Chuang SS, et al. Extranodal natural killer/T-cell lymphoma involving the gastrointestinal tract: analysis of clinical features and outcomes from the Asia Lymphoma Study Group. J Hematol Oncol 2013;6:86. Available at:

6. U.S. National Library of Medicine Key MEDLINE® Indicators Available at: http://www.nlm.nih.gov/bsd/bsd_key.html.

7. Kwong YL. Natural killer-cell malignancies: diagnosis and treatment. Leukemia 2005;19:2186-2194. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16179910.

8. Kim SJ, Kim BS, Choi CW, et al. Ki-67 expression is predictive of prognosis in patients with stage I/II extranodal NK/T-cell lymphoma, nasal type. Ann Oncol 2007;18:1382-1387. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17693651.

9. Yasuda H, Sugimoto K, Imai H, et al. Expression levels of apoptosis-related proteins and Ki-67 in nasal NK / T-cell lymphoma. Eur J Haematol 2009;82:39-45. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18778369.

10. Wong KF, Chan JK, Cheung MM, So JC. Bone marrow involvement by nasal NK cell lymphoma at diagnosis is uncommon. Am J Clin Pathol 2001;115:266-270. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11211616.

11. Chim CS, Ma ESK, Loong F, Kwong YL. Diagnostic cues for natural killer cell lymphoma: primary nodal presentation and the role of in situ hybridisation for Epstein-Barr virus encoded early small RNA in detecting occult bone marrow involvement. J Clin Pathol 2005;58:443-445. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15790718.

12. Huang W-T, Chang K-C, Huang G-C, et al. Bone marrow that is positive for Epstein-Barr virus encoded RNA-1 by in situ hybridization is related with a poor prognosis in patients with extranodal natural killer/T-cell lymphoma, nasal type. Haematologica 2005;90:1063-1069. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16079105.

13. Lee J, Suh C, Huh J, et al. Effect of positive bone marrow EBV in situ hybridization in staging and survival of localized extranodal natural killer/T-cell lymphoma, nasal-type. Clin Cancer Res 2007;13:3250-3254. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17545530.

14. Au W-Y, Pang A, Choy C, et al. Quantification of circulating Epstein-Barr virus (EBV) DNA in the diagnosis and monitoring of natural killer cell and EBV-positive lymphomas in immunocompetent patients. Blood 2004;104:243-249. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15031209.

15. Kim HS, Kim KH, Kim KH, et al. Whole blood Epstein-Barr virus DNA load as a diagnostic and prognostic surrogate: extranodal natural killer/T-cell lymphoma. Leuk Lymphoma 2009;50:757-763. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19330658.

16. Jaccard A, Gachard N, Marin B, et al. Efficacy of L-asparaginase with methotrexate and dexamethasone (AspaMetDex regimen) in patients with refractory or relapsing extranodal NK/T-cell lymphoma, a phase 2 study. Blood 2011;117:1834-1839. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21123825.

17. Suzuki R, Yamaguchi M, Izutsu K, et al. Prospective measurement of Epstein-Barr virus-DNA in plasma and peripheral blood mononuclear cells of extranodal NK/T-cell lymphoma, nasal type. Blood 2011;118:6018-6022. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21984805.

18. Ito Y, Kimura H, Maeda Y, et al. Pretreatment EBV-DNA copy number is predictive of response and toxicities to SMILE chemotherapy for extranodal NK/T-cell lymphoma, nasal type. Clin Cancer Res 2012;18:4183-4190. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22675173.

19. Liang JH, Wang L, Peter Gale R, et al. Efficacy of pegaspargase, etoposide, methotrexate and dexamethasone in newly diagnosed advanced-stage extra-nodal natural killer/T-cell lymphoma with the analysis of the prognosis of whole blood EBV-DNA. Blood Cancer J 2017;7:e608. Available at:

20. Lee J, Suh C, Park YH, et al. Extranodal natural killer T-cell lymphoma, nasal-type: a prognostic model from a retrospective multicenter study. J Clin Oncol 2006;24:612-618. Available at: http://www.ncbi.nlm.nih.gov/PubMed/16380410.

21. Kim SJ, Yoon DH, Jaccard A, et al. A prognostic index for natural killer cell lymphoma after non-anthracycline-based treatment: a multicentre, retrospective analysis. Lancet Oncol 2016;17:389-400. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26873565.

22. You JY, Chi KH, Yang MH, et al. Radiation therapy versus chemotherapy as initial treatment for localized nasal natural killer (NK)/T-cell lymphoma: a single institute survey in Taiwan. Ann Oncol 2004;15:618-625. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15033670.

23. Kim K, Chie EK, Kim CW, et al. Treatment outcome of angiocentric T-cell and NK/T-cell lymphoma, nasal type: radiotherapy versus chemoradiotherapy. Jpn J Clin Oncol 2005;35:1-5. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15681596.

24. Li Y-X, Yao B, Jin J, et al. Radiotherapy as primary treatment for stage IE and IIE nasal natural killer/T-cell lymphoma. J Clin Oncol 2006;24:181-189. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16382127.

25. Huang MJ, Jiang Y, Liu WP, et al. Early or up-front radiotherapy improved survival of localized extranodal NK/T-cell lymphoma, nasal-type in the upper aerodigestive tract. Int J Radiat Oncol Biol Phys 2008;70:166-174. Available at: http://www.ncbi.nlm.nih.gov/PubMed/17919841.

26. Chauchet A, Michallet AS, Berger F, et al. Complete remission after first-line radio-chemotherapy as predictor of survival in extranodal NK/T cell lymphoma. J Hematol Oncol 2012;5:27. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22682004.

27. Bi XW, Jiang WQ, Zhang WW, et al. Treatment outcome of patients with advanced stage natural killer/T-cell lymphoma: elucidating the effects of asparaginase and postchemotherapeutic radiotherapy. Ann Hematol 2015;94:1175-1184. Available at:

28. Bi XW, Xia Y, Zhang WW, et al. Radiotherapy and PGEMOX/GELOX regimen improved prognosis in elderly patients with early-stage extranodal NK/T-cell lymphoma. Ann Hematol 2015;94:1525-1533. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25957850.

29. Yamaguchi M, Tobinai K, Oguchi M, et al. Phase I/II study of concurrent chemoradiotherapy for localized nasal natural killer/T-cell lymphoma: Japan Clinical Oncology Group Study JCOG0211. J Clin

Oncol 2009;27:5594-5600. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19805668.

30. Yamaguchi M, Tobinai K, Oguchi M, et al. Concurrent chemoradiotherapy for localized nasal natural killer/T-cell lymphoma: an updated analysis of the Japan clinical oncology group study JCOG0211. J Clin Oncol 2012;30:4044-4046. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23045573.

31. Yamaguchi M, Suzuki R, Oguchi M, et al. Treatments and Outcomes of Patients With Extranodal Natural Killer/T-Cell Lymphoma Diagnosed Between 2000 and 2013: A Cooperative Study in Japan. J Clin Oncol 2017;35:32-39. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28034070.

32. Kim SJ, Kim K, Kim BS, et al. Phase II trial of concurrent radiation and weekly cisplatin followed by VIPD chemotherapy in newly diagnosed, stage IE to IIE, nasal, extranodal NK/T-Cell Lymphoma: Consortium for Improving Survival of Lymphoma study. J Clin Oncol 2009;27:6027-6032. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19884539.

33. Oh D, Ahn YC, Kim SJ, et al. Concurrent Chemoradiation Therapy Followed by Consolidation Chemotherapy for Localized Extranodal Natural Killer/T-Cell Lymphoma, Nasal Type. Int J Radiat Oncol Biol Phys 2015;93:677-683. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26461010.

34. Tsai HJ, Lin SF, Chen CC, et al. Long-term results of a phase II trial with frontline concurrent chemoradiotherapy followed by consolidation chemotherapy for localized nasal natural killer/T-cell lymphoma. Eur J Haematol 2015;94:130-137. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24957163.

35. Yamaguchi M, Kita K, Miwa H, et al. Frequent expression of P-glycoprotein/MDR1 by nasal T-cell lymphoma cells. Cancer 1995;76:2351-2356. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8635042.

36. Yamaguchi M, Kwong YL, Kim WS, et al. Phase II Study of SMILE Chemotherapy for Newly Diagnosed Stage IV, Relapsed, or Refractory Extranodal Natural Killer (NK)/T-Cell Lymphoma, Nasal Type: The NK-Cell Tumor Study Group Study. J Clin Oncol 2011;29:4410-4416. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21990393.

37. Kwong YL, Kim WS, Lim ST, et al. SMILE for natural killer/T-cell lymphoma: analysis of safety and efficacy from the Asia Lymphoma Study Group. Blood 2012;120:2973-2980. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22919026.

38. Lunning M, Pamer E, Maragulia J, et al. Modified SMILE (mSMILE) is Active in the Treatment of Extranodal Natural Killer/T-Cell Lymphoma: A Single Center US Experience. Clinical Lymphoma, Myeloma and Leukemia 2014;14:S143-S144. Available at: http://dx.doi.org/10.1016/j.clml.2014.06.080.

39. Qi S, Yahalom J, Hsu M, et al. Encouraging experience in the treatment of nasal type extra-nodal NK/T-cell lymphoma in a non-Asian population. Leuk Lymphoma 2016;57:2575-2583. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27183991.

40. Wang JH, Wang H, Wang YJ, et al. Analysis of the efficacy and safety of a combined gemcitabine, oxaliplatin and pegaspargase regimen for NK/T-cell lymphoma. Oncotarget 2016;7:35412-35422. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27072578.

41. Wei W, Wu P, Li L, Zhang ZH. Effectiveness of pegaspargase, gemcitabine, and oxaliplatin (P-GEMOX) chemotherapy combined with radiotherapy in newly diagnosed, stage IE to IIE, nasal-type, extranodal natural killer/T-cell lymphoma. Hematology 2017;22:320-329. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27917702.

42. Wang L, Wang ZH, Chen XQ, et al. First-line combination of GELOX followed by radiation therapy for patients with stage IE/IIE ENKTL: An updated analysis with long-term follow-up. Oncol Lett 2015;10:1036-1040. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26622621.

43. Zhang L, Jiang M, Xie L, et al. Five-year analysis from phase 2 trial of "sandwich" chemoradiotherapy in newly diagnosed, stage IE to IIE, nasal type, extranodal natural killer/T-cell lymphoma. Cancer Med 2016;5:33-40. Available at:

44. Jing XM, Zhang ZH, Wu P, et al. Efficacy and tolerance of pegaspargase, gemcitabine and oxaliplatin with sandwiched radiotherapy in the treatment of newly-diagnosed extranodal nature killer (NK)/T cell lymphoma. Leuk Res 2016;47:26-31. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27239738.

45. Li YY, Feng LL, Niu SQ, et al. Radiotherapy improves survival in early stage extranodal natural killer/T cell lymphoma patients receiving asparaginase-based chemotherapy. Oncotarget 2017;8:11480-11488. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28002792.

46. Au WY, Lie AKW, Liang R, et al. Autologous stem cell transplantation for nasal NK/T-cell lymphoma: a progress report on its value. Ann Oncol 2003;14:1673-1676. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14581277.

47. Suzuki R, Suzumiya J, Nakamura S, et al. Hematopoietic stem cell transplantation for natural killer-cell lineage neoplasms. Bone Marrow Transplant 2006;37:425-431. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16400344.

48. Lee J, Au W-Y, Park MJ, et al. Autologous hematopoietic stem cell transplantation in extranodal natural killer/T cell lymphoma: a multinational, multicenter, matched controlled study. Biol Blood Marrow Transplant 2008;14:1356-1364. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19041057.

49. Yhim HY, Kim JS, Mun YC, et al. Clinical Outcomes and Prognostic Factors of Up-Front Autologous Stem Cell Transplantation in Patients with Extranodal Natural Killer/T Cell Lymphoma. Biol Blood Marrow Transplant 2015;21:1597-1604. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25963920.

50. Lim SH, Hyun SH, Kim HS, et al. Prognostic relevance of pretransplant Deauville score on PET-CT and presence of EBV DNA in patients who underwent autologous stem cell transplantation for ENKTL. Bone Marrow Transplant 2016;51:807-812. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26855154.

51. Murashige N, Kami M, Kishi Y, et al. Allogeneic haematopoietic stem cell transplantation as a promising treatment for natural killer-cell neoplasms. Br J Haematol 2005;130:561-567. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16098071.

52. Tse E, Chan TS, Koh LP, et al. Allogeneic haematopoietic SCT for natural killer/T-cell lymphoma: a multicentre analysis from the Asia Lymphoma Study Group. Bone Marrow Transplant 2014;49:902-906. Available at:

53. Kanate AS, DiGilio A, Ahn KW, et al. Allogeneic haematopoietic cell transplantation for extranodal natural killer/T-cell lymphoma, nasal type: a CIBMTR analysis. Br J Haematol 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28771676.

54. Yokoyama H, Yamamoto J, Tohmiya Y, et al. Allogeneic hematopoietic stem cell transplant following chemotherapy containing l-asparaginase as a promising treatment for patients with relapsed or refractory extranodal natural killer/T cell lymphoma, nasal type. Leuk Lymphoma 2010;51:1509-1512. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20496989.

55. Ennishi D, Maeda Y, Fujii N, et al. Allogeneic hematopoietic stem cell transplantation for advanced extranodal natural killer/T-cell lymphoma, nasal type. Leuk Lymphoma 2011;52:1255-1261. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21599584.

56. Li M, Gao C, Li H, et al. Allogeneic haematopoietic stem cell transplantation as a salvage strategy for relapsed or refractory nasal NK/T-cell lymphoma. Med Oncol 2011;28:840-845. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20414818.

57. Suzuki R, Kako S, Hyo R, et al. Comparison of Autologous and Allogeneic Hematopoietic Stem Cell Transplantation for Extranodal NK/T-Cell Lymphoma, Nasal Type: Analysis of the Japan Society for Hematopoietic Cell Transplantation (JSHCT) Lymphoma Working Group [abstract]. Blood 2011;118:Abstract 503. Available at: http://www.bloodjournal.org/content/118/21/503.

58. Wang L, Wang WD, Xia ZJ, et al. Combination of gemcitabine, L-asparaginase, and oxaliplatin (GELOX) is superior to EPOCH or CHOP in the treatment of patients with stage IE/IIE extranodal natural killer/T cell lymphoma: a retrospective study in a cohort of 227 patients with long-term follow-up. Med Oncol 2014;31:860. Available at:

59. Wang H, Wuxiao ZJ, Zhu J, et al. Comparison of gemcitabine, oxaliplatin and L-asparaginase and etoposide, vincristine, doxorubicin, cyclophosphamide and prednisone as first-line chemotherapy in patients with stage IE to IIE extranodal natural killer/T-cell lymphoma: a multicenter retrospective study. Leuk Lymphoma 2015;56:971-977. Available at:

60. Yahalom J, Illidge T, Specht L, et al. Modern radiation therapy for extranodal lymphomas: field and dose guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys 2015;92:11-31. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25863750.

61. Khong PL, Huang B, Lee EY, et al. Midtreatment (1)(8)F-FDG PET/CT Scan for Early Response Assessment of SMILE Therapy in Natural Killer/T-Cell Lymphoma: A Prospective Study from a Single Center. J Nucl Med 2014;55:911-916. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24819420.

62. Kim SJ, Choi JY, Hyun SH, et al. Risk stratification on the basis of Deauville score on PET-CT and the presence of Epstein-Barr virus DNA after completion of primary treatment for extranodal natural killer/T-cell lymphoma, nasal type: a multicentre, retrospective analysis. Lancet Haematol 2015;2:e66-74. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26687611.

63. Jiang C, Liu J, Li L, et al. Predictive approaches for post-therapy PET/CT in patients with extranodal natural killer/T-cell lymphoma: a retrospective study. Nucl Med Commun 2017;38:937-947. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28858180.

64. Kwong YL, Chan TSY, Tan D, et al. PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing l-asparaginase. Blood 2017;129:2437-2442. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28188133.

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

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.[1] PTCL represent a relatively uncommon group of hematologic malignancies within non-Hodgkin lymphomas (NHL), accounting for about 10% of NHL cases.[2] 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%).[3]

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.[4,5] 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.[5] 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.[6] 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.[7] 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.[8] 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.[9,10] 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.[10] 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.[10]

Recent molecular and genetic studies have identified distinct subsets of ALK-negative ALCL and PTCL-NOS.[11,12] 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.[11] 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.[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.[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.[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.[3]

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® 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.[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, TCRαβ, and TCRγ. Additional IHC studies to evaluate βF1, 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, focussing 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 PTCLs 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.[26-29] 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. 58% for CHOP; *P*=0.004) with no difference in OS outcomes between the regimens.[26] 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 ≤60 years; normal LDH levels), with only 14% diagnosed with T-cell NHL (ALCL, 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).[28] 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; contrastingly, patients with higher risk IPI scores had low rates of EFS and OS with CHOP or CHOEP.[28]

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).[27] 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).[27] 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.[27]

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).[29] At a median follow-up 14 years, the EFS rates were 72% and 62.5% (*P*=.54), respectively for patients with ALK-positive ALCL and ALK-negative ALCL and the OS rates were 78.0% and 87.5%, respectively (*P*=.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. The10-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.[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).[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).[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%.[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.[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.[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.[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.[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.[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.[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 .[53-56] However, the optimal of use 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, rebiopsy 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.[57-61] 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).[57] 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.[57] 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).[58] 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).[59] 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.[61] 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, in one retrospective analysis when the outcomes were analyzed by major PTCL subtypes, the EFS rates were inferior in patients with PTCL-NOS (23%, *P* = 0.028) and patients with ALCL had a non-significant trend towards improved EFS rates (67%, *P* = 0.41).[58]

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.[62-65] In a phase II study, Corradini et al investigated the role of RIC allogeneic SCT in patients with relapsed or refractory PTCL (N=17).[62] 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%.[62] 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.[63] The 5-year transplant-related mortality (TRM) rate was 34%; TRM at 100 days was 21%. Patients had previously received a median of 2 prior therapies (range, 1-5), and 74% had received myeloablative conditioning prior to transplantation.[63] 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).[64] 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.[64] 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.[65] 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.[65] 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.[66] 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).[67] 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 or 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.[74,75] 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.[76,77] 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).[77] 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%; response assessed by an independent central review). While the study was not 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 subytpes (32% and 35% respectively for PTCL-NOS and ALCL).[77] 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%).[78] 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.[78] 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.[79-83] 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%]).[80] 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.[81] 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 [81] The most common grade ≥3 adverse events included thrombocytopenia (24%), neutropenia (20%), and infections (19% for any; including pneumonia [5%] and sepsis [5%]).[80] The BELIEF trial evaluated belinostat in 129 patients with relapsed or refractory PTCL (pretreated with more than one prior systemic therapy).[83] 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%.[83] 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 0r 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.[84] 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.[85] 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.[86] 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.[86]

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.[87-90] Aggressive second-line chemotherapy with ICE followed by HDT/ASCR was evaluated in patients with relapsed/refractory PTCL.[87] 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).[87] 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.[88] 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.[89] 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 %.[90]

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.[84-86] 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.[83] Bendamustine also induced higher response rates in patients with AITL compared to those with other subtypes.[78] Pralatrexate has very limited activity in AITL compared to other subtypes.[77] However, the aforementioned studies were not sufficiently powered to evaluate the response rates in specific subtypes.[77,78,83] Cyclosporine has been effective in patients with relapsed AITL following treatment with steroid or multiagent chemotherapy or HDT/ASCR.[74,75]

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.[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.[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.[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.[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.[99,102,105]

T-cell Large Granular Lymphocytic Leukemia

The discussion section for T-cell large granular lymphocytic leukemia is currently under development.

References

1. Savage KJ. Peripheral T-cell lymphomas. Blood Rev 2007;21:201-216. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17512649.

2. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 1997;89:3909-3918. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9166827.

3. Vose J, Armitage J, Weisenburger D. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol 2008;26:4124-4130. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18626005.

4. Gisselbrecht C, Gaulard P, Lepage E, et al. Prognostic significance of T-cell phenotype in aggressive non-Hodgkin's lymphomas. Groupe d'Etudes des Lymphomes de l'Adulte (GELA). Blood 1998;92:76-82. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9639502.

5. Savage KJ, Chhanabhai M, Gascoyne RD, Connors JM. Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification. Ann Oncol 2004;15:1467-1475. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15367405.

6. Mourad N, Mounier N, Briere J, et al. Clinical, biologic, and pathologic features in 157 patients with angioimmunoblastic T-cell lymphoma treated within the Groupe d'Etude des Lymphomes de l'Adulte (GELA) trials. Blood 2008;111:4463-4470. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18292286.

7. Falini B, Pileri S, Zinzani PL, et al. ALK+ lymphoma: clinico-pathological findings and outcome. Blood 1999;93:2697-2706. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10194450.

8. Weisenburger DD, Savage KJ, Harris NL, et al. Peripheral T-cell lymphoma, not otherwise specified: a report of 340 cases from the International Peripheral T-cell Lymphoma Project. Blood 2011;117:3402-3408. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21270441.

9. Gascoyne RD, Aoun P, Wu D, et al. Prognostic significance of anaplastic lymphoma kinase (ALK) protein expression in adults with anaplastic large cell lymphoma. Blood 1999;93:3913-3921. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10339500.

10. Savage KJ, Harris NL, Vose JM, et al. ALK- anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. Blood 2008;111:5496-5504. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18385450.

11. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24894770.

12. Iqbal J, Wright G, Wang C, et al. Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma. Blood 2014;123:2915-2923. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24632715.

13. Gale J, Simmonds PD, Mead GM, et al. Enteropathy-type intestinal T-cell lymphoma: clinical features and treatment of 31 patients in a single center. J Clin Oncol 2000;18:795-803. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10673521.

14. Daum S, Ullrich R, Heise W, et al. Intestinal non-Hodgkin's lymphoma: a multicenter prospective clinical study from the German Study Group on Intestinal non-Hodgkin's Lymphoma. J Clin Oncol 2003;21:2740-2746. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12860953.

15. Wohrer S, Chott A, Drach J, et al. Chemotherapy with cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone (CHOEP) is not effective in patients with enteropathy-type intestinal T-cell lymphoma. Ann Oncol 2004;15:1680-1683. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15520071.

16. Babel N, Paragi P, Chamberlain RS. Management of enteropathy-associated T-cell lymphoma: an algorithmic approach. Case Rep Oncol 2009;2:36-43. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20740143.

17. Lopez-Guillermo A, Cid J, Salar A, et al. Peripheral T-cell lymphomas: initial features, natural history, and prognostic factors in a series of 174 patients diagnosed according to the R.E.A.L. Classification. Ann Oncol 1998;9:849-855. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9789607.

18. Abramson JS, Feldman T, Kroll-Desrosiers AR, et al. Peripheral T-cell lymphomas in a large US multicenter cohort: prognostication in the modern era including impact of frontline therapy. Ann Oncol 2014;25:2211-2217. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25193992.

19. Gallamini A, Stelitano C, Calvi R, et al. Peripheral T-cell lymphoma unspecified (PTCL-U): a new prognostic model from a retrospective multicentric clinical study. Blood 2004;103:2474-2479. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14645001.

20. Jaffe ES. Pathobiology of Peripheral T-cell Lymphomas. Hematology 2006;2006:317-322. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17124078.

21. Dupuis J, Boye K, Martin N, et al. Expression of CXCL13 by neoplastic cells in angioimmunoblastic T-cell lymphoma (AITL): a new diagnostic marker providing evidence that AITL derives from follicular helper T cells. Am J Surg Pathol 2006;30:490-494. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16625095.

22. Grogg KL, Attygalle AD, Macon WR, et al. Expression of CXCL13, a chemokine highly upregulated in germinal center T-helper cells, distinguishes angioimmunoblastic T-cell lymphoma from peripheral T-cell lymphoma, unspecified. Mod Pathol 2006;19:1101-1107. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16680156.

23. Greer JP. Therapy of Peripheral T/NK Neoplasms. Hematology 2006:331-337. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17124080.

24. Horwitz SM. Management of peripheral T-cell non-Hodgkin's lymphoma. Curr Opin Oncol 2007;19:438-443. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17762567.

25. Simon A, Peoch M, Casassus P, et al. Upfront VIP-reinforced-ABVD (VIP-rABVD) is not superior to CHOP/21 in newly diagnosed peripheral T cell lymphoma. Results of the randomized phase III trial GOELAMS-LTP95. Br J Haematol 2010;151:159-166. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20738307.

26. Pfreundschuh M, Trumper L, Kloess M, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: results of the NHL-B1 trial of the DSHNHL. Blood 2004;104:626-633. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14982884.

27. Escalon MP, Liu NS, Yang Y, et al. Prognostic factors and treatment of patients with T-cell non-Hodgkin lymphoma: the M. D. Anderson Cancer Center experience. Cancer 2005;103:2091-2098. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15816054.

28. Schmitz N, Trumper L, Ziepert M, et al. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood 2010;116:3418-3425. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20660290.

29. Dunleavy K, Pittaluga S, Shovlin M, et al. Phase II trial of dose-adjusted EPOCH in untreated systemic anaplastic large cell lymphoma. Haematologica 2016;101:e27-29. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26518748.

30. Blystad AK, Enblad G, Kvaloy S, et al. High-dose therapy with autologous stem cell transplantation in patients with peripheral T cell lymphomas. Bone Marrow Transplant 2001;27:711-716. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11360110.

31. Jantunen E, Wiklund T, Juvonen E, et al. Autologous stem cell transplantation in adult patients with peripheral T-cell lymphoma: a nation-wide survey. Bone Marrow Transplant 2004;33:405-410. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14676776.

32. Yamazaki T, Sawada U, Kura Y, et al. Treatment of high-risk peripheral T-cell lymphomas other than anaplastic large-cell lymphoma with a dose-intensified CHOP regimen followed by high-dose chemotherapy. A single institution study. Acta Haematol 2006;116:90-95. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16914902.

33. Feyler S, Prince HM, Pearce R, et al. The role of high-dose therapy and stem cell rescue in the management of T-cell malignant lymphomas: a BSBMT and ABMTRR study. Bone Marrow Transplant 2007;40:443-450. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17589529.

34. Kim MK, Kim S, Lee SS, et al. High-dose chemotherapy and autologous stem cell transplantation for peripheral T-cell lymphoma: complete response at transplant predicts survival. Ann Hematol 2007;86:435-442. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17256144.

35. Rodriguez J, Conde E, Gutierrez A, et al. The results of consolidation with autologous stem-cell transplantation in patients with peripheral T-cell lymphoma (PTCL) in first complete remission: the Spanish Lymphoma and Autologous Transplantation Group experience. Ann Oncol 2007;18:652-657. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17229774.

36. Yang DH, Kim WS, Kim SJ, et al. Prognostic factors and clinical outcomes of high-dose chemotherapy followed by autologous stem cell transplantation in patients with peripheral T cell lymphoma, unspecified: complete remission at transplantation and the prognostic index of peripheral T cell lymphoma are the major factors predictive of outcome. Biol Blood Marrow Transplant 2009;15:118-125. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19135950.

37. Corradini P, Tarella C, Zallio F, et al. Long-term follow-up of patients with peripheral T-cell lymphomas treated up-front with high-dose chemotherapy followed by autologous stem cell transplantation. Leukemia 2006;20:1533-1538. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16871285.

38. Rodriguez J, Conde E, Gutierrez A, et al. Frontline autologous stem cell transplantation in high-risk peripheral T-cell lymphoma: a prospective study from The Gel-Tamo Study Group. Eur J Haematol 2007;79:32-38. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17598836.

39. Mercadal S, Briones J, Xicoy B, et al. Intensive chemotherapy (high-dose CHOP/ESHAP regimen) followed by autologous stem-cell transplantation in previously untreated patients with peripheral T-cell lymphoma. Ann Oncol 2008;19:958-963. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18303032.

40. Reimer P, Rudiger T, Geissinger E, et al. Autologous stem-cell transplantation as first-line therapy in peripheral T-cell lymphomas: results of a prospective multicenter study. J Clin Oncol 2009;27:106-113. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19029417.

41. d'Amore F, Relander T, Lauritzsen GF, et al. Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. J Clin Oncol 2012;30:3093-3099. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22851556.

42. d'Amore F, Relander T, Lauritzsen GF, et al. Ten years median follow-up of the NORDIC NLG-T-01 trial on CHOEP and upfront autologous transplantation in peripheral T-cell lymphomas [abstract]. Hematological Oncology 2015;33 (Suppl S1):Abstract 074. Available at: http://onlinelibrary.wiley.com/doi/10.1002/hon.2227/epdf.

43. Corradini P, Vitolo U, Rambaldi A, et al. Intensified chemo-immunotherapy with or without stem cell transplantation in newly diagnosed patients with peripheral T-cell lymphoma. Leukemia 2014;28:1885-1891. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24662801.

44. d'Amore F, Leppa S, da Silva MG, et al. First Interim Efficacy and Safety Analysis of an International Phase III Randomized Trial in Newly Diagnosed Systemic Peripheral T-Cell Lymphoma Treated with Chemotherapy with or without Alemtuzumab and Consolidated by High Dose Therapy [abstract]. Blood 2012;120:Abstract 57. Available at: http://www.bloodjournal.org/content/120/21/57.

45. Trumper LH, Wulf G, Ziepert M, et al. Alemtuzumab added to CHOP for treatment of peripheral T-cell lymphoma (pTNHL) of the elderly: Final results of 116 patients treated in the international ACT-2 phase III trial. J Clin Oncol 2016;34:7500. Available at: http://meeting.ascopubs.org/cgi/content/abstract/34/15_suppl/7500.

46. Schetelig J, Fetscher S, Reichle A, et al. Long-term disease-free survival in patients with angioimmunoblastic T-cell lymphoma after high-dose chemotherapy and autologous stem cell transplantation. Haematologica 2003;88:1272-1278. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14607756.

47. Kyriakou C, Canals C, Goldstone A, et al. High-dose therapy and autologous stem-cell transplantation in angioimmunoblastic lymphoma: complete remission at transplantation is the major determinant of Outcome-Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 2008;26:218-224. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18182664.

48. Rodriguez J, Conde E, Gutierrez A, et al. Prolonged survival of patients with angioimmunoblastic T-cell lymphoma after high-dose chemotherapy and autologous stem cell transplantation: the GELTAMO experience. Eur J Haematol 2007;78:290-296. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17378891.

49. Bishton MJ, Haynes AP. Combination chemotherapy followed by autologous stem cell transplant for enteropathy-associated T cell lymphoma. Br J Haematol 2007;136:111-113. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17116129.

50. Sieniawski M, Angamuthu N, Boyd K, et al. Evaluation of enteropathy-associated T-cell lymphoma comparing standard therapies with a novel regimen including autologous stem cell transplantation. Blood 2010;115:3664-3670. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20197551.

51. Ellin F, Landstrom J, Jerkeman M, Relander T. Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry. Blood 2014;124:1570-1577. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25006130.

52. Nijeboer P, de Baaij LR, Visser O, et al. Treatment response in enteropathy associated T-cell lymphoma; survival in a large multicenter cohort. Am J Hematol 2015;90:493-498. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25716069.

53. Pellegrini C, Argnani L, Broccoli A, et al. Prognostic value of interim positron emission tomography in patients with peripheral T-cell lymphoma. Oncologist 2014;19:746-750. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24869930.

54. El-Galaly TC, Pedersen MB, Hutchings M, et al. Utility of interim and end-of-treatment PET/CT in peripheral T-cell lymphomas: A review of 124 patients. Am J Hematol 2015;90:975-980. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26201505.

55. Horwitz S, Coiffier B, Foss F, et al. Utility of (1)(8)fluoro-deoxyglucose positron emission tomography for prognosis and response assessments in a phase 2 study of romidepsin in patients with relapsed or refractory peripheral T-cell lymphoma. Ann Oncol 2015;26:774-779. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25605745.

56. Tomita N, Hattori Y, Fujisawa S, et al. Post-therapy (1)(8)F-fluorodeoxyglucose positron emission tomography for predicting outcome in patients with peripheral T cell lymphoma. Ann Hematol 2015;94:431-436. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25338967.

57. Rodriguez J, Caballero MD, Gutierrez A, et al. High-dose chemotherapy and autologous stem cell transplantation in peripheral T-cell lymphoma: the GEL-TAMO experience. Ann Oncol 2003;14:1768-1775. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14630683.

58. Song KW, Mollee P, Keating A, Crump M. Autologous stem cell transplant for relapsed and refractory peripheral T-cell lymphoma: variable outcome according to pathological subtype. Br J Haematol 2003;120:978-985. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12648067.

59. Kewalramani T, Zelenetz AD, Teruya-Feldstein J, et al. Autologous transplantation for relapsed or primary refractory peripheral T-cell lymphoma. Br J Haematol 2006;134:202-207. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16759221.

60. Rodriguez J, Conde E, Gutierrez A, et al. The adjusted International Prognostic Index and beta-2-microglobulin predict the outcome after autologous stem cell transplantation in relapsing/refractory peripheral T-cell lymphoma. Haematologica 2007;92:1067-1074. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17640855.

61. Chen AI, McMillan A, Negrin RS, et al. Long-term results of autologous hematopoietic cell transplantation for peripheral T cell lymphoma: the Stanford experience. Biol Blood Marrow Transplant 2008;14:741-747. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18541192.

62. Corradini P, Dodero A, Zallio F, et al. Graft-versus-lymphoma effect in relapsed peripheral T-cell non-Hodgkin's lymphomas after reduced-intensity conditioning followed by allogeneic transplantation of hematopoietic cells. J Clin Oncol 2004;22:2172-2176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15169805.

63. Le Gouill S, Milpied N, Buzyn A, et al. Graft-versus-lymphoma effect for aggressive T-cell lymphomas in adults: a study by the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire. J Clin Oncol 2008;26:2264-2271. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18390969.

64. Kyriakou C, Canals C, Finke J, et al. Allogeneic stem cell transplantation is able to induce long-term remissions in angioimmunoblastic T-cell lymphoma: a retrospective study from the lymphoma working party of the European group for blood and marrow transplantation. J Clin Oncol 2009;27:3951-3958. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19620487.

65. Dodero A, Spina F, Narni F, et al. Allogeneic transplantation following a reduced-intensity conditioning regimen in relapsed/refractory peripheral T-cell lymphomas: long-term remissions and response to donor lymphocyte infusions support the role of a graft-versus-lymphoma effect. Leukemia 2012;26:520-526. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21904377.

66. Smith SM, Burns LJ, van Besien K, et al. Hematopoietic cell transplantation for systemic mature T-cell non-Hodgkin lymphoma. J Clin Oncol 2013;31:3100-3109. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23897963.

67. Beitinjaneh A, Saliba RM, Medeiros LJ, et al. Comparison of survival in patients with T cell lymphoma after autologous and allogeneic stem cell transplantation as a frontline strategy or in relapsed disease. Biol

Blood Marrow Transplant 2015;21:855-859. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25652691.

68. Enblad G, Hagberg H, Erlanson M, et al. A pilot study of alemtuzumab (anti-CD52 monoclonal antibody) therapy for patients with relapsed or chemotherapy-refractory peripheral T-cell lymphomas. Blood 2004;103:2920-2924. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15070664.

69. Zinzani PL, Alinari L, Tani M, et al. Preliminary observations of a phase II study of reduced-dose alemtuzumab treatment in patients with pretreated T-cell lymphoma. Haematologica 2005;90:702-703. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15921394.

70. Zinzani PL, Venturini F, Stefoni V, et al. Gemcitabine as single agent in pretreated T-cell lymphoma patients: evaluation of the long-term outcome. Ann Oncol 2010;21:860-863. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19887465.

71. Zinzani PL, Musuraca G, Tani M, et al. Phase II trial of proteasome inhibitor bortezomib in patients with relapsed or refractory cutaneous T-cell lymphoma. J Clin Oncol 2007;25:4293-4297. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17709797.

72. Toumishey E, Prasad A, Dueck G, et al. Final report of a phase 2 clinical trial of lenalidomide monotherapy for patients with T-cell lymphoma. Cancer 2015;121:716-723. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25355245.

73. Morschhauser F, Fitoussi O, Haioun C, et al. A phase 2, multicentre, single-arm, open-label study to evaluate the safety and efficacy of single-agent lenalidomide (Revlimid) in subjects with relapsed or refractory peripheral T-cell non-Hodgkin lymphoma: the EXPECT trial. Eur J Cancer 2013;49:2869-2876. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23731832.

74. Advani R, Horwitz S, Zelenetz A, Horning SJ. Angioimmunoblastic T cell lymphoma: treatment experience with cyclosporine. Leuk Lymphoma 2007;48:521-525. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17454592.

75. Wang X, Zhang D, Wang L, et al. Cyclosporine treatment of angioimmunoblastic T-cell lymphoma relapsed after an autologous hematopoietic stem cell transplant. Exp Clin Transplant 2015;13:203-205. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24918480.

76. O'Connor OA, Horwitz S, Hamlin P, et al. Phase II-I-II study of two different doses and schedules of pralatrexate, a high-affinity substrate for the reduced folate carrier, in patients with relapsed or refractory lymphoma reveals marked activity in T-cell malignancies. J Clin Oncol 2009;27:4357-4364. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19652067.

77. O'Connor OA, Pro B, Pinter-Brown L, et al. Pralatrexate in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma: Results From the Pivotal PROPEL Study. J Clin Oncol 2011;29:1182-1189. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21245435.

78. Damaj G, Gressin R, Bouabdallah K, et al. Results from a prospective, open-label, phase II trial of bendamustine in refractory or relapsed T-cell lymphomas: the BENTLY trial. J Clin Oncol 2013;31:104-110. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23109692.

79. Piekarz RL, Frye R, Prince HM, et al. Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma. Blood 2011;117:5827-5834. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21355097.

80. Coiffier B, Pro B, Prince HM, et al. Results From a Pivotal, Open-Label, Phase II Study of Romidepsin in Relapsed or Refractory Peripheral T-Cell Lymphoma After Prior Systemic Therapy. J Clin Oncol 2012;30:631-636. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22271479.

81. Coiffier B, Pro B, Prince HM, et al. Romidepsin for the treatment of relapsed/refractory peripheral T-cell lymphoma: pivotal study update

demonstrates durable responses. J Hematol Oncol 2014;7:11. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24456586.

82. Foss F, Advani R, Duvic M, et al. A Phase II trial of Belinostat (PXD101) in patients with relapsed or refractory peripheral or cutaneous T-cell lymphoma. Br J Haematol 2015;168:811-819. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25404094.

83. O'Connor OA, Horwitz S, Masszi T, et al. Belinostat in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma: Results of the Pivotal Phase II BELIEF (CLN-19) Study. J Clin Oncol 2015;33:2492-2499. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26101246.

84. Pro B, Advani R, Brice P, et al. Brentuximab Vedotin (SGN-35) in Patients With Relapsed or Refractory Systemic Anaplastic Large-Cell Lymphoma: Results of a Phase II Study. J Clin Oncol 2012;30:2190-2196. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22614995.

85. Pro B, Advani R, Brice P, et al. Four-year survival data from an ongoing pivotal phase 2 study of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma [abstract]. Blood 2014;124:Abstract 3095. Available at: http://www.bloodjournal.org/content/124/21/3095.abstract.

86. Horwitz SM, Advani RH, Bartlett NL, et al. Objective responses in relapsed T-cell lymphomas with single-agent brentuximab vedotin. Blood 2014;123:3095-3100. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24652992.

87. Horwitz S, Moskowitz C, Kewalramani T, et al. Second-line therapy with ICE followed by high dose therapy and autologous stem cell transplantation for relapsed/refractory peripheral T-cell lymphomas: minimal benefit when analyzed by intent to treat [abstract]. Blood 2005;106:Abstract 2679. Available at: http://www.bloodjournal.org/content/106/11/2679.

88. Connors JM, Sehn LH, Villa D, et al. Gemcitabine, Dexamethasone, and Cisplatin (GDP) As Secondary Chemotherapy In Relapsed/Refractory Peripheral T-Cell Lymphoma. Blood 2013;122:4345-4345. Available at: http://www.bloodjournal.org/content/122/21/4345.abstract.

89. Park BB, Kim WS, Suh C, et al. Salvage chemotherapy of gemcitabine, dexamethasone, and cisplatin (GDP) for patients with relapsed or refractory peripheral T-cell lymphomas: a consortium for improving survival of lymphoma (CISL) trial. Ann Hematol 2015;94:1845-1851. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26251158.

90. Qian Z, Song Z, Zhang H, et al. Gemcitabine, navelbine, and doxorubicin as treatment for patients with refractory or relapsed T-cell lymphoma. Biomed Res Int 2015;2015:606752. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25866797.

91. Cohen PL, Brooks JJ. Lymphomas of the breast. A clinicopathologic and immunohistochemical study of primary and secondary cases. Cancer 1991;67:1359-1369. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1991299.

92. Talwalkar SS, Miranda RN, Valbuena JR, et al. Lymphomas involving the breast: a study of 106 cases comparing localized and disseminated neoplasms. Am J Surg Pathol 2008;32:1299-1309. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18636016.

93. Validire P, Capovilla M, Asselain B, et al. Primary breast non-Hodgkin's lymphoma: a large single center study of initial characteristics, natural history, and prognostic factors. Am J Hematol 2009;84:133-139. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19199367.

94. de Jong D, Vasmel WL, de Boer JP, et al. Anaplastic large-cell lymphoma in women with breast implants. JAMA 2008;300:2030-2035. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18984890.

95. Roden AC, Macon WR, Keeney GL, et al. Seroma-associated primary anaplastic large-cell lymphoma adjacent to breast implants: an

indolent T-cell lymphoproliferative disorder. Mod Pathol 2008;21:455-463. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18223553.

96. Carty MJ, Pribaz JJ, Antin JH, et al. A patient death attributable to implant-related primary anaplastic large cell lymphoma of the breast. Plast Reconstr Surg 2011;128:112e-118e. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21775924.

97. Lazzeri D, Agostini T, Bocci G, et al. ALK-1-negative anaplastic large cell lymphoma associated with breast implants: a new clinical entity. Clin Breast Cancer 2011;11:283-296. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21729665.

98. Popplewell L, Thomas SH, Huang Q, et al. Primary anaplastic large-cell lymphoma associated with breast implants. Leuk Lymphoma 2011;52:1481-1487. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21699454.

99. Miranda RN, Aladily TN, Prince HM, et al. Breast implant-associated anaplastic large-cell lymphoma: long-term follow-up of 60 patients. J Clin Oncol 2014;32:114-120. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24323027.

100. Brody GS, Deapen D, Taylor CR, et al. Anaplastic large cell lymphoma occurring in women with breast implants: analysis of 173 cases. Plast Reconstr Surg 2015;135:695-705. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25490535.

101. U.S. Food and Drug Administration Anaplastic Large Cell Lymphoma (ALCL) In Women with Breast Implants: Preliminary FDA Findings and Analyses. 2011. Available at: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm239996.htm. Accessed November 2011.

102. Thompson PA, Prince HM. Breast implant-associated anaplastic large cell lymphoma: a systematic review of the literature and mini-meta analysis. Curr Hematol Malig Rep 2013;8:196-210. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23765424.

103. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26628470.

104. Laurent C, Delas A, Gaulard P, et al. Breast implant-associated anaplastic large cell lymphoma: two distinct clinicopathological variants with different outcomes. Ann Oncol 2016;27:306-314. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26598546.

105. Aladily TN, Medeiros LJ, Amin MB, et al. Anaplastic large cell lymphoma associated with breast implants: a report of 13 cases. Am J Surg Pathol 2012;36:1000-1008. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22613996.