National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

T-Cell Lymphomas

Version 4.2024 — May 28, 2024

NCCN.org

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

NCCN Guidelines for Patients® available at www.nccn.org/patients

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NCCN Guidelines Panel Disclosures

ξ Bone marrow transplantation
ϖ Dermatology
‡ Hematology/Hematology oncology
Þ Internal medicine
† Medical oncology
≠ Pathology
¥ Patient advocacy
ʘ Plastic surgery
§ Radiotherapy/Radiation oncology
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Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

Updates in Version 4.2024 of the NCCN Guidelines for T-Cell Lymphomas from Version 3.2024 include:

• Suggested treatment regimen references were updated throughout the guidelines.

Discussion

MS-1

• The full discussion section was updated to reflect changes in the algorithm.

Updates in Version 3.2024 of the NCCN Guidelines for T-Cell Lymphomas from Version 2.2024 include:

Discussion

MS-1

• The following sections of the Discussion were updated to reflect changes in the algorithm: Breast Implant-Associated ALCL, T-Cell Large Granular Lymphocytic Leukemia and Adult T-Cell Leukemia/Lymphoma

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Updates in Version 2.2024 of the NCCN Guidelines for T-Cell Lymphomas from Version 1.2024 include:

T-Cell Large Granular Lymphocytic Leukemia

LGLL-2

• Additional therapy after no response to first-line therapy, ruxolitinib added as a category 2A recommendation.
• Second-line therapy after progressive or refractory disease to all first-line therapies, ruxolitinib (if not previously used) added as a category 2A, preferred recommendation.
• Footnote s added: In the phase II studies, ruxolitinib was dosed at 20 mg BID. Due to the prevalence of cytopenias in patients with LGLL, dose reductions to 10 or 5 mg BID can be considered. Frequent CBC monitoring is recommended. (Moskowitz A, et al. Blood 2021;138:2828-2837; Moskowitz A, et al. Blood 2023;142:Abstract 183)

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Updates in Version 1.2024 of the NCCN Guidelines for T-Cell Lymphomas from Version 1.2023 include:

Global changes

• Suggested treatment regimen references were updated throughout the guidelines.

Peripheral T-Cell Lymphomas

PTCL-1

• Diagnosis,
  ▸ Essential (Immunophenotyping),
    ◊ 2nd sub-bullet revised by adding TRBC1 to the flow cytometry panel
    ◊ 3rd sub-bullet added: T-follicular helper [TFH] cell markers (CXCL13, ICOS) if PTCL not otherwise specified (PTCL-NOS) of TFH phenotype is suspected
  ▸ Useful,
    ◊ 3rd bullet added: Consider next-generation sequencing (NGS) panel to support the diagnosis of TFH subtypes
    ◊ 5th bullet revised: Additional immunohistochemical studies to characterize subsets of PTCL including ~~markers of T-follicular helper [TFH] cell origin (CXCL13, ICOS, PD1) and~~ cytotoxic T-cell markers (TIA-1, granzyme B, perforin)

PTCL-B 2 of 8

• Initial palliative intent therapy for PTCL-NOS; EATL; MEITL and AITL, including Nodal PTCL, TFH, and FTCL and AITL
  ▸ For all subtypes, duvelisib moved from other recommended regimens to preferred regimens.
  ▸ For ALK+ ALCL only, brigatinib and ceritinib added as category 2A, other recommended options.
  ▸ For AITL, NODAL PTCL, TFH, and FTCL only, azacitidine (PO/IV/SC) added as a category 2B, other recommended option.

PTCL-B 3 of 8

• Second-line therapy and subsequent therapy for PTCL-NOS; EATL; MEITL
  ▸ For both intention to proceed to transplant and no intention to proceed to transplant,
    ◊ Duvelisib moved from other recommended regimens to preferred regimens.
    ◊ Brentuximab vedotin and bendamustine for CD30+ PTCL added as a category 2B, other recommended option.

PTCL-B 4 of 8

• Second-line therapy and subsequent therapy for AITL, INCLUDING NODAL PTCL, TFH, and FTCL
  ▸ For both intention to proceed to transplant and no intention to proceed to transplant,
    ◊ Duvelisib moved from other recommended regimens to preferred regimens.
    ◊ Brentuximab vedotin and bendamustine for CD30+ PTCL added as a category 2B, other recommended option.
    ◊ Azacitidine (PO/IV/SC) added as a category 2B, other recommended option.

PTCL-B 5 of 8

• Second-line therapy and subsequent therapy for ALCL
  ▸ For both intention to proceed to transplant and no intention to proceed to transplant,
    ◊ Brentuximab vedotin and bendamustine for CD30+ PTCL added as a category 2B, other recommended option.
    ◊ For ALK+ ALCL only, brigatinib, ceritinib, and lorlatinib added as category 2A, other recommended option.
• Footnotes
  ▸ Footnote p added: Dosing for oral azacitidine differs from that of intravenous or subcutaneous azacitidine.
  ▸ Footnote q revised: ~~Alectinib has~~ *Second-generation (alectinib, brigatinib, ceritinib) and third-generation (lorlatinib) ALK inhibitors have* shown activity in patients with CNS involvement.

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UPDATES

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Updates in Version 1.2024 of the NCCN Guidelines for T-Cell Lymphomas from Version 1.2023 include:

Breast Implant-Associated ALCL

BIAA-1
• Workup, breast MRI, "with and without contrast" added.

BIAA-A
• Systemic therapy regimens preference stratified.

T-Cell Large Granular Lymphocytic Leukemia

LGLL-1
• Footnote a revised: Approximately 10% of LGLL cases will be of the NK-cell subtype (~~chronic NK-cell lymphocytosis~~ *chronic lymphoproliferative disorder of NK cells [ICC]; NK-large granular lymphocytic leukaemia [WHO])* ~~included as a provisional entity in the WHO classification~~. *These are* treated with a similar approach to T-LGLL.

LGLL-2
• Indications for treatment, added: ANC <1500 with documented T-LGLL and recurrent infections

T-Cell Prolymphocytic Leukemia

TPLL-2
• First- and second-line regimens moved to TPLL-A

TPLL-A
• Second-line therapy or subsequent therapy,
  ▸ Ruxolitinib added as a category 2A, other recommended regimen.
  ▸ Retreatment with alemtuzumab (IV) ± pentostatin moved from Other recommended regimens to Useful in certain circumstances.

Adult T-Cell Leukemia/Lymphoma

ATLL-1
• Diagnosis, Useful
  ▸ 3rd bullet added: Cell surface marker analysis by flow cytometry for CCR4
  ▸ 4th bullet added: Consider NGS panel
• Workup, Useful, 3rd bullet added: CRP, soluble interleukin-2 receptor (sIL-2R), serum albumin and blood urea nitrogen (BUN)
• Chronic and smoldering recommendations separated

ATLL-2
• Smoldering recommendations separated by "Asymptomatic (no skin lesions, no opportunistic infections)" and "Symptomatic (skin lesions/tumors opportunistic infections)"
• Footnotes moved to TCLYM-B: "Consider prophylaxis for tumor lysis syndrome (See TCLYM-B) and "Anti-infective prophylaxis: Pneumocystis jiroveci pneumonia (PJP) prophylaxis with sulfamethoxazole/trimethoprim or equivalent screening and treatment (if needed) for strongyloidiasis." (Also for ATLL-3 and ATLL-4)
• Footnote n revised: ~~Peginterferon alfa-2a may be substituted for other interferon preparations. (Schiller M, et al. J Eur Acad Dermatol Venereol 2017;31:1841-1847.)~~ *Peginterferon alfa-2a is the only interferon available for clinical use in the US and it may be substituted for other interferon preparations.(Schiller M, et al. J Eur Acad Dermatol Venerol 2017;31:1841-1847; Patsatsi A et al. J Eur Acad Dermatol Venereol 2022;36:e291-e293; Osman S, et al. Dermatologic Therapy 2023*.

ATLL-3
• Chronic recommendations separated by "Low risk (sIL-2R <1000 U/mL)/Intermediate risk (sIL-2R 1000-6000 U/mL)" and "High risk (elevated LDH, low albumin, high BUN, sIL-2R >6000 U/mL)."

ATLL-4
• Acute, no response, additional therapy, options clarified from, "Alternate therapy not previously treated with: Second-line therapy (ATLL-D) or Zidovudine and interferon" to "Alternate regimens not used in first-line therapy or Second-line therapy (ATLL-D)"
• Footnote q added: Modified Prognostic Index for Aggressive ATLL (ATLL-C).
• Footnote r revised: ... Allogeneic ~~hematopoietic cell transplant may cure a portion of patients~~ *HCT may be a curative option for some patients*.
• Footnote s revised: CNS *disease is common and* prophylaxis is ~~strongly~~ recommended.

ATLL-C
• Added: Modified Prognostic Index for Aggressive ATLL.

ATLL-D 1 of 2
• Footnote d added: Lenalidomide and mogamulizumab may be associated with higher incidences of GVHD after allogeneic HCT.

Continued

Updates in Version 1.2024 of the NCCN Guidelines for T-Cell Lymphomas from Version 1.2023 include:

Hepatosplenic T-Cell Lymphoma
HSTCL-3
- Footnote j revised by adding references: Voss MH et al. Clin Lymphoma Myeloma Leuk 2013;13:8-14; Klebaner D et al. Clin Lymphoma Myeloma Leuk 2020;20:431-437 e432. (also for HTSCL-A)
- Footnote removed: Consider asparaginase-based combination chemotherapy regimen (ENKL-B 1 of 3).

Extranodal NK/T-Cell Lymphomas
ENKL-B 1 of 3
- Combined modality therapy, Sandwich chemoradiation,
  - Preferred regimens, added: GELAD (gemcitabine, etoposide, pegaspargase, dexamethasone) x 2 cycles followed by RT followed by 2 cycles of GELAD as a category 2A recommendation.

Supportive Care
TCLYM-B 2 of 4
- Hemophagocytic Lymphohistiocytosis (HLH)
  - Management, 2nd sub-bullet revised by adding: Start with HLH-directed therapy if cytopenias preclude standard anti-lymphoma therapy, and then initiate standard anti-lymphoma therapy when cytopenias improve.
  - Footnotes
    - ◊ Footnote c added: Consider optimized HLH inflammatory (OHI) index (combined elevation of sCD25 (>3900 U/mL) and ferritin (>1000 ng/mL) to simplify the diagnosis of HLH in patients with hematologic malignancies (Zoref-Lorenz A, et al. Blood 2022;139:1098-1111).
    - ◊ Footnote d added: La Rosée P, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood 2019;133:2465-2477; Setiadi A, et al. Malignancy-associated haemophagocytic lymphohistiocytosis. Lancet Haematol 2022;9:e217-e227.

TCLYM-B 3 of 4
- Monoclonal Antibody (mAb) Therapy and Viral Reactivation,
  - Anti-infective prophylaxis, 3rd sub-bullet added: Consider screening and treatment (if needed) for strongyloidiasis in patients with ATLL.
  - Bullet removed: Anti-CD20 Antibody Therapy - See NCCN Guidelines for B-Cell Lymphomas

Principles of Radiation Therapy
TCLYM-D 4 of 4
- Sandwich chemoradiation, 2nd sub-bullet added: GELAD (2 cycles) followed by RT 50-56 Gy followed by GELAD (2 cycles)

Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of NK/T-Cell Neoplasms
TCLYM-E
- Section moved from Guidelines for B-Cell Lymphomas to the Guidelines for T-Cell Lymphomas.

DIAGNOSIS[a]

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 peripheral T-cell lymphomas (PTCL). Rebiopsy if consult material is nondiagnostic.**
- **Excisional or incisional biopsy is preferred over core needle biopsy. A fine-needle aspiration (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[b]**
  - **Immunohistochemistry (IHC) panel may include CD20, CD3, CD10, BCL6, Ki-67, CD5, CD30, CD2, CD4, CD8, CD7, CD56, CD21, CD23, TCRβ, TCRδ, PD1/CD279, ALK, TP63 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; TCRαβ, TCRɣδ, TRBC1**
  - **T-follicular helper [TFH] cell markers (CXCL13, ICOS) if PTCL not otherwise specified (PTCL-NOS) of TFH phenotype is suspected**
- **Epstein-Barr encoding region in situ hybridization (EBER-ISH)**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **Molecular analysis to detect clonal *TCR* gene rearrangements or other assessment of clonality[c]**
- **Consider molecular analysis to detect *DUSP22* rearrangement if anaplastic large cell lymphoma (ALCL), ALK negative[a]; *TP63* rearrangement if IHC is positive for *TP63***
- **Consider next-generation sequencing (NGS) panel to support the diagnosis of TFH subtypes[a]**
- **Additional immunohistochemical studies to characterize subsets of PTCL including cytotoxic T-cell markers (TIA-1, granzyme B, perforin)**
- **Assessment of human T-cell lymphotropic virus (HTLV)-1/2[d] by serology or other methods is encouraged, as results can impact therapy.**

→ **Diagnostic subtypes (PTCL-2)**

[a] Principles of Molecular Analysis in T-Cell Lymphomas (TCLYM-A).
[b] Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (TCLYM-E).
[c] Clonal *TCR* gene rearrangements alone are not sufficient for diagnosis, as these can also be seen in patients with non-malignant conditions. Results should be interpreted in the context of overall presentation. See Principles of Molecular Analysis in T-Cell Lymphomas (TCLYM-A).
[d] See map for prevalence of HTLV-1/2 by geographic region. HTLV-1/2 has been described in patients in non-endemic areas.

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

SUBTYPES

Subtypes included:[e]
- **PTCL-NOS**
- **Enteropathy-associated T-cell lymphoma (EATL)**
- **Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)**[f]
- **ALCL, ALK positive**
- **ALCL, ALK negative**
- **Angioimmunoblastic T-cell lymphoma (AITL)/(follicular helper T-cell lymphoma [TFH lymphoma], angioimmunoblastic type [ICC]/nodal TFH cell lymphoma, angioimmunoblastic-type [WHO5])**[g]
- ***Nodal PTCL with TFH phenotype (nodal PTCL, TFH)*/TFH lymphoma, NOS (ICC)/nodal TFH cell lymphoma (WHO5)**
- **Follicular T-cell lymphoma (FTCL)/TFH lymphoma, follicular type (ICC)/nodal TFH cell lymphoma, follicular-type (WHO5)**

→ Workup (PTCL-3)

- **All other T-cell lymphomas**
  - **Breast implant-associated ALCL (BIA-ALCL)** → BIAA-1
  - **T-cell large granular lymphocytic leukemia (T-LGLL)** → LGLL-1
  - **Adult T-cell leukemia/lymphoma (ATLL)** → ATLL-1
  - **T-cell prolymphocytic leukemia (T-PLL)** → TPLL-1
  - **Extranodal natural killer (NK)/T-cell lymphoma (ENKL)** → ENKL-1
  - **Hepatosplenic T-cell lymphoma (HSTCL)** → HSTCL-1

Subtypes not included:
- **Primary cutaneous ALCL (NCCN Guidelines for Primary Cutaneous Lymphomas)**

[e] Primary cutaneous PTCLs with limited skin involvement may have an indolent disease course, are very heterogeneous, and the optimal management may not be along these guidelines.
[f] MEITL has only recently been separated as its own entity and optimal treatment has not been defined.
[g] AITL may occasionally present with concurrent diffuse large B-cell lymphoma (DLBCL) and Epstein-Barr virus (EBV) and appropriate IHC should be performed. Clonal hematopoiesis in AITL is considered as a risk factor for cardiovascular disease.

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

WORKUP

ESSENTIAL:
- History and physical (H&P) examination; full skin examination; attention to node-bearing areas, including Waldeyer's ring; evaluation of size of liver and spleen, nasopharynx
- Performance status
- B symptoms
- Complete blood count (CBC) with differential
- Bone marrow biopsy ± aspirate
- Lactate dehydrogenase (LDH)
- Comprehensive metabolic panel
- Uric acid
- Fluorodeoxyglucose (FDG)-PET/CT scan[h] (preferred) and/or chest/abdominal/pelvic (C/A/P) CT with contrast of diagnostic quality
- Calculation of International Prognostic Index (IPI)[i]
- Echocardiogram or multigated acquisition (MUGA) scan if anthracycline-based regimen is indicated
- Pregnancy testing in those of childbearing potential (if chemotherapy or RT is planned)

USEFUL IN CERTAIN CIRCUMSTANCES:
- Neck CT with contrast
- Head CT or MRI with contrast
- Consider central nervous system (CNS) evaluation, if clinical signs/symptoms[j]
- Skin biopsy
- HIV testing
- Hepatitis B and C testing
- Consider quantitative Epstein-Barr virus (EBV) polymerase chain reaction (PCR)
- Consider evaluating for celiac disease in patients with newly diagnosed EATL
- Assessment of HTLV-1/2 by serology or other methods is encouraged, if not previously done, as results can impact therapy[d]
- Discuss fertility preservation[k]

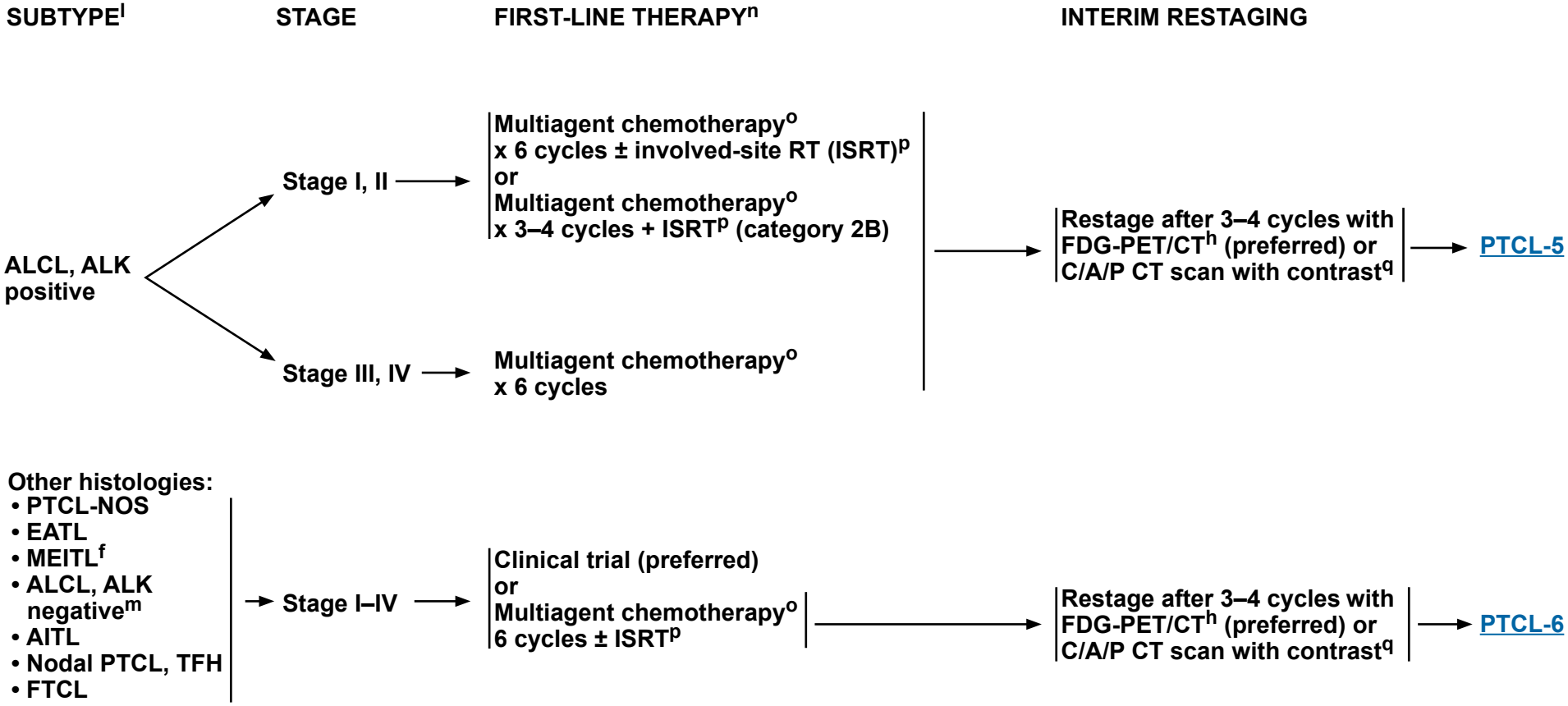
SUBTYPES

- ALCL, ALK positive → PTCL-4
- PTCL-NOS
- EATL
- MEITL
- ALCL, ALK negative
- AITL
- Nodal PTCL, TFH
- FTCL

→ PTCL-4

[d] See map for prevalence of HTLV-1/2 by geographic region. HTLV-1/2 has been described in patients in non-endemic areas.
[h] Patients with T-cell lymphomas often have extranodal disease, which may be inadequately imaged by CT. PET scan is preferred.
[i] International Prognostic Index (PTCL-A).
[j] The role of intrathecal prophylaxis in PTCL is largely unknown.
[k] Fertility preservation options include: sperm banking, semen cryopreservation, in vitro fertilization (IVF), or ovarian tissue or oocyte cryopreservation.

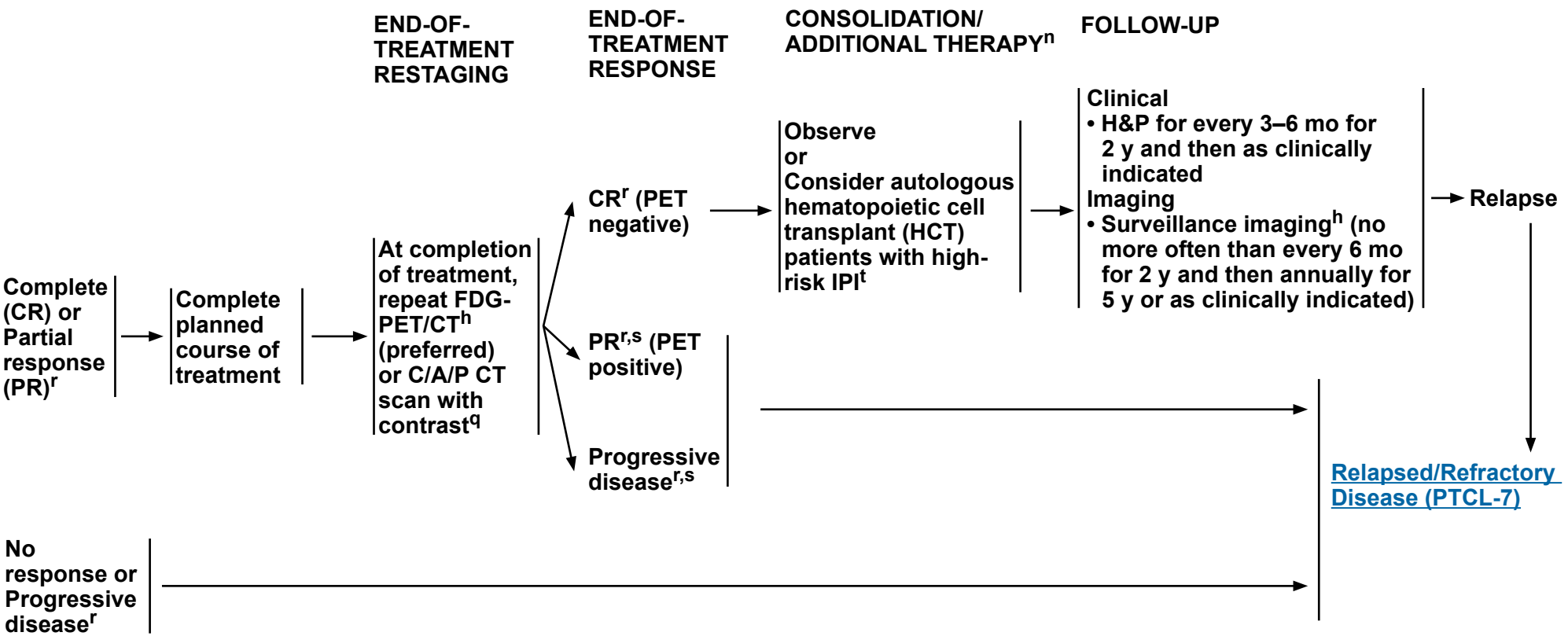
Note: All recommendations are category 2A unless otherwise indicated.



[f] MEITL has only recently been separated as its own entity and optimal treatment has not been defined.
[h] Patients with T-cell lymphomas often have extranodal disease, which may be inadequately imaged by CT. PET scan is preferred.
[l] For selected patients, palliative therapy for symptom management may be considered. See PTCL-B 2 of 8 for palliative treatment options.
[m] ALCL, ALK-negative with a *DUSP22* rearrangement has been variably associated with a prognosis more similar to ALK-positive disease and treatment according to the ALCL, ALK-positive algorithm may be considered for ALK-negative ALCL with *DUSP22* rearrangement (Parrilla Castellar ER, et al. Blood 2014;124:1473-1480; Pedersen MB, et al. Blood 2017;130:554-557; Hapgood G, et al. Br J Haematol 2019;186:e28-e31).
[n] Consider prophylaxis for tumor lysis syndrome (TLS) (TCLYM-B).
[o] Suggested Treatment Regimens (PTCL-B).
[p] Principles of Radiation Therapy (TCLYM-D).
[q] Other baseline imaging studies relevant for response assessment should be repeated as well.

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

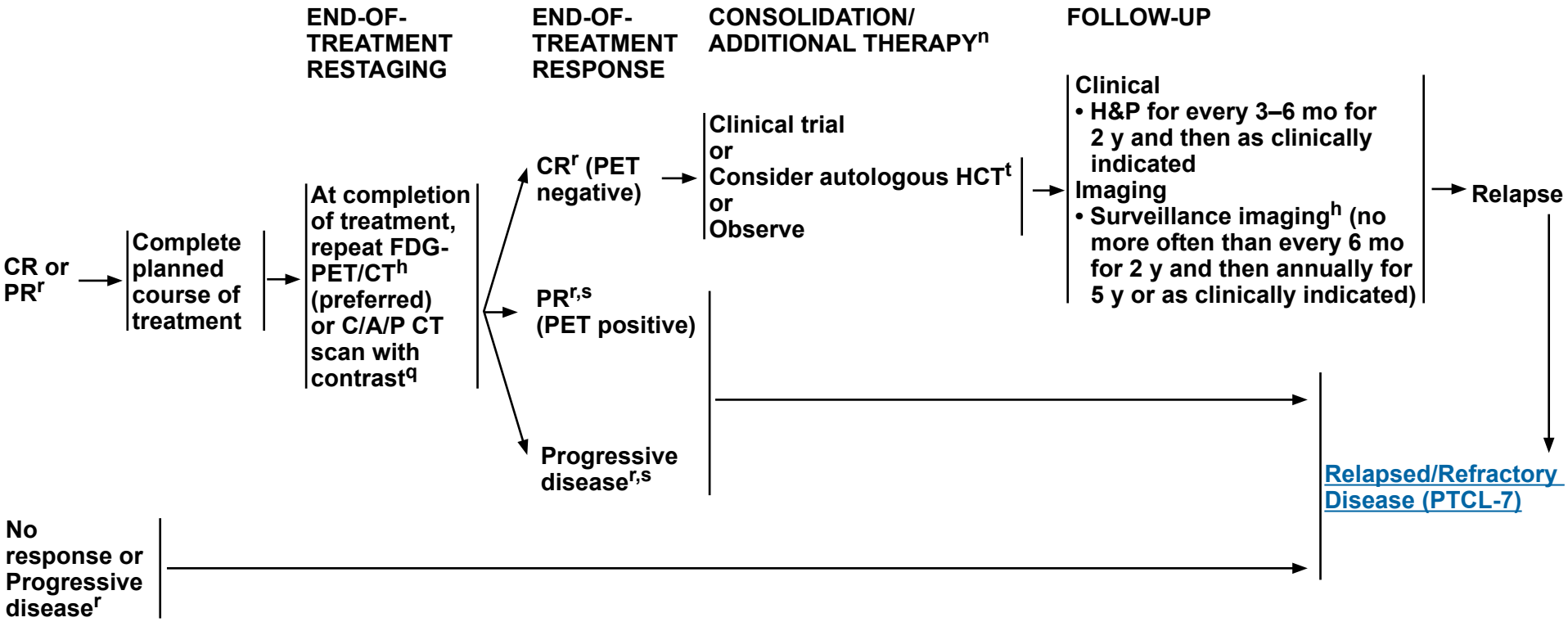
ALCL, ALK-POSITIVE: ADDITIONAL THERAPY BASED ON RESPONSE



[h] Patients with T-cell lymphomas often have extranodal disease, which may be inadequately imaged by CT. PET scan is preferred.
[n] Consider prophylaxis for TLS (TCLYM-B).
[q] Other baseline imaging studies relevant for response assessment should be repeated as well.
[r] Lugano Response Criteria for Non-Hodgkin Lymphoma (TCLYM-C).
[s] Repeat biopsy should be considered (strongly consider for AITL since it may occasionally present with concurrent DLBCL) for persistent or new PET-positive lesions prior to additional therapy.
[t] Localized areas can be irradiated before or after autologous HCT. See Principles of Radiation Therapy (TCLYM-D).

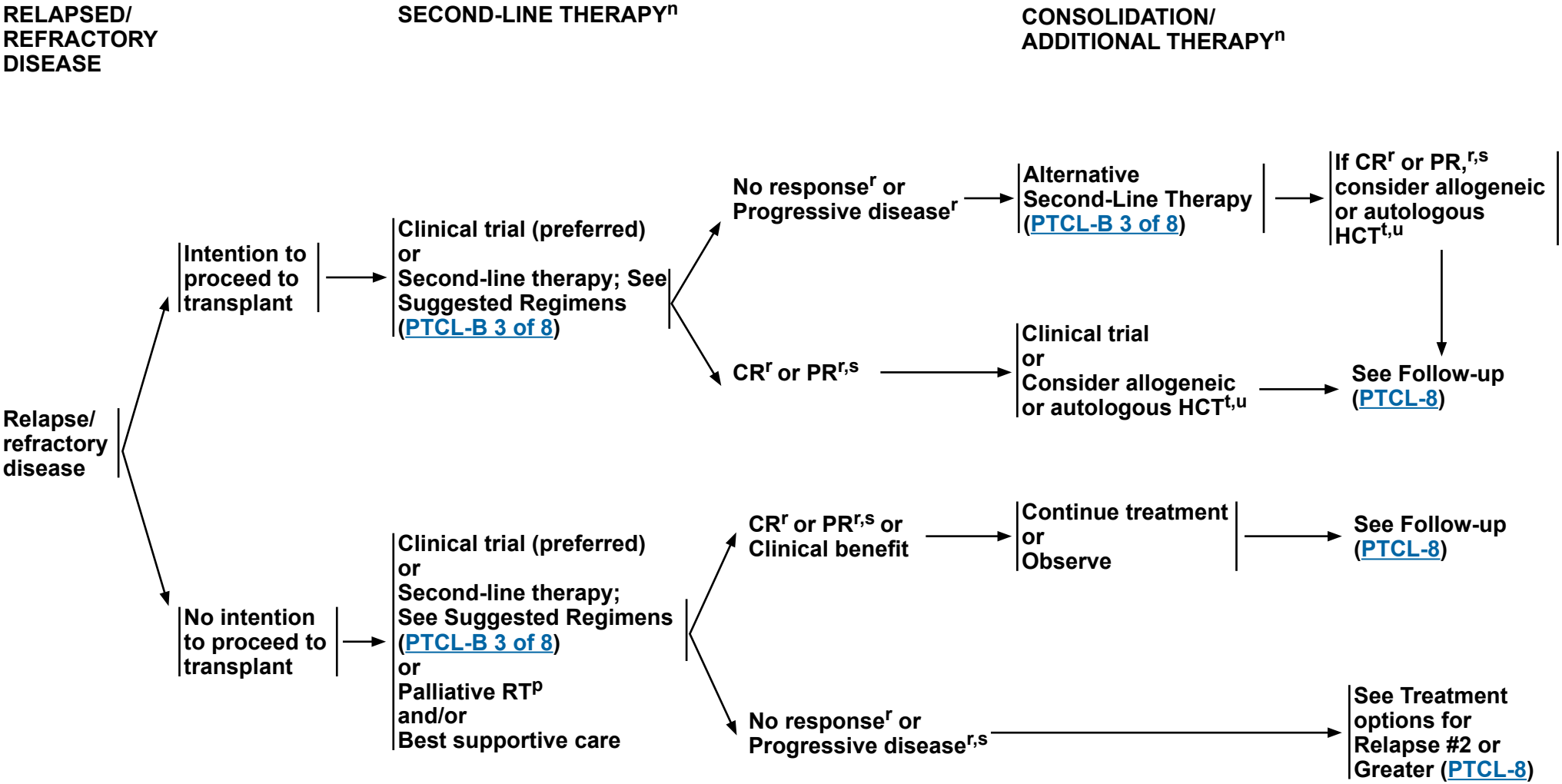
Note: All recommendations are category 2A unless otherwise indicated.

OTHER HISTOLOGIES: ADDITIONAL THERAPY BASED ON RESPONSE



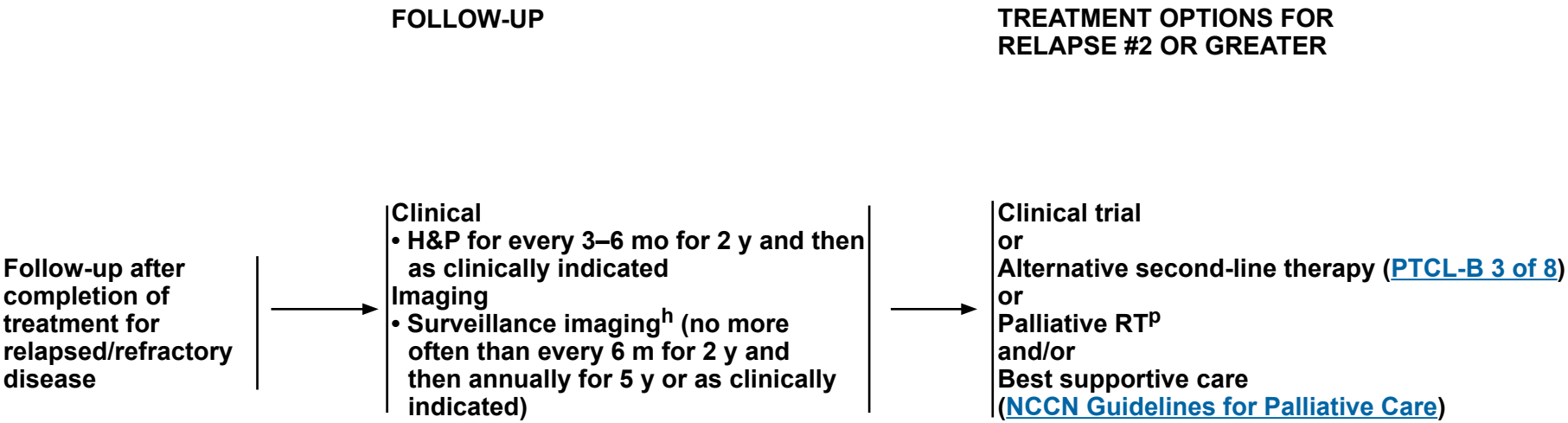
[h] Patients with T-cell lymphomas often have extranodal disease, which may be inadequately imaged by CT. PET scan is preferred.
[n] Consider prophylaxis for TLS (TCLYM-B).
[q] Other baseline imaging studies relevant for response assessment should be repeated as well.
[r] Lugano Response Criteria for Non-Hodgkin Lymphoma (TCLYM-C).
[s] Repeat biopsy should be considered (strongly consider for AITL since it may occasionally present with concurrent DLBCL) for persistent or new PET-positive lesions prior to additional therapy.
[t] Localized areas can be irradiated before or after autologous HCT. See Principles of Radiation Therapy (TCLYM-D).

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



[n] Consider prophylaxis for TLS (TCLYM-B).
[p] Principles of Radiation Therapy (TCLYM-D).
[r] Lugano Response Criteria for Non-Hodgkin Lymphoma (TCLYM-C).
[s] Repeat biopsy should be considered (strongly consider for AITL since it may occasionally present with concurrent DLBCL) for persistent or new PET-positive lesions prior to additional therapy.
[t] Localized areas can be irradiated before or after HCT. See Principles of Radiation Therapy (TCLYM-D).
[u] Allogeneic HCT is recommended in this setting.

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



[h] Patients with T-cell lymphomas often have extranodal disease, which may be inadequately imaged by CT. PET scan is preferred.
[p] Principles of Radiation Therapy (TCLYM-D).

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

INTERNATIONAL PROGNOSTIC INDEX (ALL PATIENTS)[a]

ALL PATIENTS:	RISK GROUPS:	
• 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		

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

RISK FACTORS:	RISK GROUPS:	
• 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

AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX[a]

PATIENTS ≤60 YEARS:	RISK GROUPS:	
• 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 (modified-PIT)[c]

RISK FACTORS:	RISK GROUPS:	
• Age >60 years	• Group 1	0 or 1
• Serum LDH > normal	• Group 2	2
• ECOG Performance Status 2–4	• Group 3	3 or 4
• Ki-67 ≥80%		

T-CELL SCORE (INTERNATIONAL T-CELL LYMPHOMA PROJECT)[d]

RISK FACTORS:	RISK GROUPS:	
• Stage III–IV	• Low risk	0
• ECOG Performance Status 2–4	• Intermediate risk	1–2
• Serum albumin <35 g/L	• High risk	3–4
• Absolute neutrophil count (ANC) >6.5 x 10^9/L		

[a] 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] Federico M, Bellei M, Marcheselli L, et al. Peripheral T cell lymphoma, not otherwise specified (PTCL-NOS). A new prognostic model developed by the International T cell Project Network. Br J Haematol 2018;181:760-769.

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

SUGGESTED TREATMENT REGIMENS[a,b]

FIRST-LINE THERAPY[c]	
ALCL[d]	**Preferred regimen** • Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone)[e] (category 1) **Other recommended regimens** • CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) • CHOEP[f] (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone) • Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin)
Other histologies (PTCL-NOS; EATL; MEITL[g]; AITL; nodal PTCL, TFH; and FTCL)	**Preferred regimens** (alphabetical order) • Brentuximab vedotin + CHP for CD30+ histologies[e,h] • CHOEP[f] • CHOP • Dose-adjusted EPOCH **Other recommended regimens** (alphabetical order) • CHOP followed by IVE (ifosfamide, etoposide, and epirubicin) alternating with intermediate-dose methotrexate (Newcastle Regimen; studied only in patients with EATL)[i] • HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine (category 3)

FIRST-LINE CONSOLIDATION
• Consider consolidation with autologous HCT

Footnotes on PTCL-B 6 of 8

See Initial Palliative-Intent Therapy (PTCL-B 2 of 8)
See Second-line and Subsequent Therapy:
• PTCL-NOS; EATL; MEITL; FTCL (PTCL-B 3 of 8)
• AITL, including nodal PTCL, TFH (PTCL-B 4 of 8)
• ALCL (PTCL-B 5 of 8)

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

SUGGESTED TREATMENT REGIMENS[a,b]

INITIAL PALLIATIVE-INTENT THERAPY

PTCL-NOS; EATL; MEITL[g]	AITL, NODAL PTCL, TFH, and FTCL	ALCL

Preferred regimens (regimens in alphabetical order)
• Clinical trial
• Belinostat
• Brentuximab vedotin for CD30+ PTCL[e,h]
• Duvelisib[j]
• Pralatrexate
• Romidepsin
 	
Other recommended regimens (alphabetical order by category)
• Alemtuzumab[k]
• Bendamustine[e]
• Cyclophosphamide and/or etoposide (IV or PO)
• Gemcitabine
• Lenalidomide[e]
• RT[l]
• Bortezomib[m] (category 2B)
• Ruxolitinib (category 2B)
	Preferred regimens (regimens in alphabetical order)
	• Clinical trial
	• Belinostat
	• Brentuximab vedotin for CD30+ AITL[e,h]
	• Duvelisib[j]
	• Romidepsin
	
	Other recommended regimens (alphabetical order by category)
	• Alemtuzumab[k]
	• Bendamustine[e]
	• Cyclophosphamide and/or etoposide (IV or PO)
	• Cyclosporine[n]
	• Gemcitabine
	• Lenalidomide[e]
	• Pralatrexate[o]
	• RT[l]
	• Azacitidine (PO/IV/SC)[p] (category 2B)
	• Bortezomib[m] (category 2B)
	• Ruxolitinib (category 2B)
		Preferred regimen (regimens in alphabetical order)
		• Clinical trial
		• Brentuximab vedotin[e]
		
		Other recommended regimens (alphabetical order by category)
		• ALK inhibitors (for ALK-positive ALCL only):[q]
		  ▸ Alectinib
		  ▸ Brigatinib
		  ▸ Ceritinib
		  ▸ Crizotinib
		• Belinostat
		• Bendamustine[e]
		• Cyclophosphamide and/or etoposide (IV or PO)
		• Duvelisib[j]
		• Gemcitabine
		• Pralatrexate
		• RT[l]
		• Romidepsin
		• Bortezomib[m] (category 2B)
		• Ruxolitinib (category 2B)

Footnotes on PTCL-B 6 of 8

See First-line Therapy on PTCL-B 1 of 8.

See Second-line and Subsequent Therapy:
PTCL-NOS; EATL; MEITL (PTCL-B 3 of 8)
AITL, including nodal PTCL, TFH, and FTCL (PTCL-B 4 of 8)
ALCL (PTCL-B 5 of 8)

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

SUGGESTED TREATMENT REGIMENS[a,b]
PTCL-NOS; EATL; MEITL[g]

SECOND-LINE THERAPY AND SUBSEQUENT THERAPY (INTENTION TO PROCEED TO TRANSPLANT)

Preferred regimens (regimens in alphabetical order)
- Clinical trial
- Single agents (alphabetical order)
  - Belinostat
  - Brentuximab vedotin for CD30+ PTCL[e,h]
  - Duvelisib[j]
  - Pralatrexate
  - Romidepsin
- Combination regimens (alphabetical order)
  - DHA (dexamethasone and cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin)
  - ESHA (etoposide, methylprednisolone, and cytarabine) + platinum (cisplatin or oxaliplatin)
  - GDP (gemcitabine, dexamethasone, and cisplatin)
  - GemOx (gemcitabine and oxaliplatin)
  - ICE (ifosfamide, carboplatin, and etoposide)

Other recommended regimens (alphabetical order by category)
- Single agents
  - Bendamustine[e]
  - Gemcitabine
  - Lenalidomide[e]
  - Ruxolitinib (category 2B)
- Combination regimens
  - Brentuximab vedotin and bendamustine for CD30+ PTCL[e,h] (category 2B)
  - GVD (gemcitabine, vinorelbine, and liposomal doxorubicin)[q]

SECOND-LINE AND SUBSEQUENT THERAPY (NO INTENTION TO PROCEED TO TRANSPLANT)

Preferred regimens (regimens in alphabetical order)
- Clinical trial
- Belinostat
- Brentuximab vedotin for CD30+ PTCL[e,h]
- Duvelisib[j]
- Pralatrexate
- Romidepsin

Other recommended regimens (alphabetical order by category)
- Single agents
  - Alemtuzumab[k]
  - Bendamustine[e]
  - Cyclophosphamide and/or etoposide (IV or PO)
  - Gemcitabine
  - Lenalidomide[e]
  - RT[l]
  - Bortezomib[m] (category 2B)
  - Ruxolitinib (category 2B)
- Combination regimen
  - Brentuximab vedotin and bendamustine for CD30+ PTCL[e,h] (category 2B)

Footnotes on PTCL-B 6 of 8

See First-line Therapy on PTCL-B 1 of 8.

See Second-line and Subsequent Therapy:
AITL, including nodal PTCL, TFH, and FTCL (PTCL-B 4 of 8)
ALCL (PTCL-B 5 of 8)

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

SUGGESTED TREATMENT REGIMENS[a,b]
AITL, NODAL PTCL, TFH, AND FTCL

SECOND-LINE THERAPY AND SUBSEQUENT THERAPY (INTENTION TO PROCEED TO TRANSPLANT)

Preferred regimens (regimens in alphabetical order)
- Clinical trial
- Single agents (alphabetical order)
  - Belinostat
  - Brentuximab vedotin for CD30+ AITL[e,h]
  - Duvelisib[j]
  - Romidepsin
- Combination regimens (alphabetical order)
  - DHA (dexamethasone and cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin)
  - ESHA (etoposide, methylprednisolone, and cytarabine) + platinum (cisplatin or oxaliplatin)
  - GDP (gemcitabine, dexamethasone, and cisplatin)
  - GemOx (gemcitabine and oxaliplatin)
  - ICE (ifosfamide, carboplatin, and etoposide)

Other recommended regimens (alphabetical order by category)
- Single agents
  - Azacitidine (PO/IV/SC)[p]
  - Bendamustine[e]
  - Gemcitabine
  - Lenalidomide[e]
  - Pralatrexate[o]
  - Ruxolitinib (category 2B)
- Combination regimens
  - GVD (gemcitabine, vinorelbine, and liposomal doxorubicin)[r]
  - Brentuximab vedotin and bendamustine for CD30+ PTCL[e,h] (category 2B)

SECOND-LINE AND SUBSEQUENT THERAPY (NO INTENTION TO PROCEED TO TRANSPLANT)

Preferred regimens (regimens in alphabetical order)
- Clinical trial
- Belinostat
- Brentuximab vedotin for CD30+ AITL[e,h]
- Duvelisib[j]
- Romidepsin

Other recommended regimens (alphabetical order by category)
- Single agents
  - Alemtuzumab[k]
  - Azacitidine (PO/IV/SC)[p]
  - Bendamustine[e]
  - Cyclophosphamide and/or etoposide (IV or PO)
  - Cyclosporine[n]
  - Gemcitabine
  - Lenalidomide[e]
  - Pralatrexate[o]
  - RT[l]
  - Bortezomib[m] (category 2B)
  - Ruxolitinib (category 2B)
- Combination regimen
  - Brentuximab vedotin and bendamustine for CD30+ PTCL[e,h] (category 2B)

Footnotes on PTCL-B 6 of 8

See First-line Therapy on PTCL-B 1 of 8.

See Second-line and Subsequent Therapy:
PTCL-NOS; EATL; MEITL (PTCL-B 3 of 8)
ALCL (PTCL-B 5 of 8)

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

SUGGESTED TREATMENT REGIMENS[a,b]
ALCL

SECOND-LINE THERAPY AND SUBSEQUENT THERAPY (WITH INTENTION TO PROCEED TO TRANSPLANT)

Preferred regimen
- Clinical trial
- Brentuximab vedotin[e]

Other recommended regimens (alphabetical order by category)
- Single agents
  - ALK inhibitors (for ALK-positive ALCL only):[q]
    - ◊ Alectinib
    - ◊ Brigatinib
    - ◊ Ceritinib
    - ◊ Crizotinib
    - ◊ Lorlatinib
  - Belinostat
  - Bendamustine[e]
  - Duvelisib[j]
  - Gemcitabine
  - Pralatrexate
  - Romidepsin
  - Ruxolitinib (category 2B)
- Combination regimens
  - DHA (dexamethasone and cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin)
  - ESHA (etoposide, methylprednisolone, and cytarabine) + platinum (cisplatin or oxaliplatin)
  - GDP (gemcitabine, dexamethasone, and cisplatin)
  - GVD (gemcitabine, vinorelbine, and liposomal doxorubicin)[q]
  - GemOx (gemcitabine and oxaliplatin)
  - ICE (ifosfamide, carboplatin, and etoposide)
  - Brentuximab vedotin and bendamustine[e] (category 2B)

SECOND-LINE AND SUBSEQUENT THERAPY (NO INTENTION TO PROCEED TO TRANSPLANT)

Preferred regimen
- Clinical trial
- Brentuximab vedotin[e]

Other recommended regimens (alphabetical order by category)
- Single agents
  - ALK inhibitors (for ALK-positive ALCL only):[q]
    - ◊ Alectinib
    - ◊ Brigatinib
    - ◊ Ceritinib
    - ◊ Crizotinib
    - ◊ Lorlatinib
  - Belinostat
  - Bendamustine[e]
  - Cyclophosphamide and/or etoposide (IV or PO)
  - Duvelisib[j]
  - Gemcitabine
  - Pralatrexate
  - RT[l]
  - Romidepsin
  - Bortezomib[j] (category 2B)
  - Ruxolitinib (category 2B)
- Combination regimen
  - Brentuximab vedotin and bendamustine[e] (category 2B)

Footnotes on PTCL-B 6 of 8

See First-line Therapy on PTCL-B 1 of 8.

See Second-line and Subsequent Therapy:
PTCL-NOS; EATL; MEITL (PTCL-B 3 of 8)
AITL, including nodal PTCL, TFH, and FTCL (PTCL-B 4 of 8)

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

SUGGESTED TREATMENT REGIMENS FOOTNOTES

[a] See references for regimens on PTCL-B 7 of 8 and PTCL-B 8 of 8.
[b] Consider prophylaxis for TLS (TCLYM-B).
[c] While anthracycline-based regimens confer a favorable prognosis in ALCL, ALK-positive, 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.
[d] ALCL, ALK-negative with a *DUSP22* rearrangement has been variably associated with a prognosis more similar to ALK-positive disease and treatment according to the ALCL, ALK-positive algorithm may be considered (Parrilla Castellar ER, et al. Blood 2014;124:1473-1480; Hapgood G, et al. Br J Haematol 2019;186:e28-e31; Pedersen MB, et al. Blood 2017;130:554-557).
[e] Supportive Care (TCLYM-B).
[f] Oral etoposide dose of 200 mg/m^2 (PO dosing of etoposide is 2x the IV dose) may be substituted on day 2 and 3 for IV etoposide. Consider splitting the daily doses of oral etoposide over 200 mg.
[g] MEITL has only recently been separated as its own entity and optimal treatment has not been defined.
[h] Interpretation of CD30 expression is not universally standardized. Responses have been seen in patients with a low level of CD30 positivity.
[i] CHOP followed by IVE regimen includes HCT.
[j] In the phase II study, the preferred dosing regimen of duvelisib was 75 mg BID for 2 cycles followed by 25 mg BID for long-term disease control.
[k] While alemtuzumab is no longer commercially available, it may be obtained for clinical use. Cytomegalovirus (CMV) monitoring or prophylaxis is recommended (TCLYM-B).
[l] Principles of Radiation Therapy (TCLYM-D).
[m] Activity has been demonstrated in small clinical trials and additional larger trials are needed.
[n] With close follow-up of renal function.
[o] In AITL, pralatrexate has limited activity.
[p] Dosing for oral azacitidine differs from that of IV or SC azacitidine.
[q] Second-generation (ie, alectinib, brigatinib, ceritinib) and third-generation (lorlatinib) ALK inhibitors have shown activity in patients with CNS involvement.
[r] Data suggest there may be excessive pulmonary toxicity with GVD (gemcitabine, vinorelbine, and liposomal doxorubicin) regimen when used in combination with unconjugated anti-CD30 monoclonal antibodies for the treatment of Hodgkin lymphoma (Blum KA, 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 to 4 weeks following treatment with brentuximab vedotin before initiation.

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

SUGGESTED TREATMENT REGIMENS
REFERENCES

First-Line Therapy

Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone)

Horwitz S, O'Connor OA, Pro B, et al. The ECHELON-2 Trial: 5-year results of a randomized, phase III study of brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma. Ann Oncol 2022;33:288-298.

CHOEP

Cederleuf H, Bjerregard Pedersen M, Jerkeman M, et al. The addition of etoposide to CHOP is associated with improved outcome in ALK+ adult anaplastic large cell lymphoma: A Nordic Lymphoma Group study. Br J Haematol 2017;178:739-746.

Schmitz N, Trümper 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.

Dose-adjusted EPOCH

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-e29.

Maeda Y, Nishimori H, Yoshida I, et al. Dose-adjusted EPOCH chemotherapy for untreated peripheral T-cell lymphomas: a multicenter phase II trial of West-JHOG PTCL0707. Haematologica 2017;102:2097-2103.

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.

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

ALK inhibitors

Alectinib

Fukano R, Mori T, Sekimizu M, et al. Alectinib for relapsed or refractory anaplastic lymphoma kinase-positive anaplastic large cell lymphoma: an open-label phase II trial. Cancer Sci 2020;111:4540-4547.

Brigatinib

Veleanu L, Tesson B, Lamant L, et al. Brigatinib in patients with ALK-positive anaplastic large cell lymphoma who have failed brentuximab vedotin. Hematological Oncology 2023;41:505-506.

Ceritinib

Richly H, Kim TM, Schuler M, et al. Ceritinib in patients with advanced anaplastic lymphoma kinase-rearranged anaplastic large-cell lymphoma. Blood 2015;126:1257-1258.

Crizotinib

Gambacorti Passerini C, Farina F, Stasia A, et al. Crizotinib in advanced, chemoresistant anaplastic lymphoma kinase-positive lymphoma patients. J Natl Cancer Inst 2014;106:djt378.

Bossi E, Aroldi A, Brioschi F, et al. Phase two study of crizotinib in patients with anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma relapsed/refractory to chemotherapy Am J Hematol 2020;95:E319-E321.

Lorlatinib

Ripamonti A, Aroldi A, Cocito F, et al. Preliminary Results of Phase 2 Open Label Study of Lorlatinib Monotherapy in Relapsed/Refractory ALK + Lymphomas Previously Treated with Other Tyrosine Kinase Inhibitors [abstract]. Blood 2023;142: Abstract 4474

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.

Azacitidine

Dupuis J, Tsukasaki K, Bachy E, et al. Oral azacytidine in patients with relapsed/refractory angioimmunoblastic T-cell lymphoma: Final analysis of the Oracle phase III study [abstract]. Blood 2022;140(suppl 1):2310-2312.

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.

Continued

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

SUGGESTED TREATMENT REGIMENS
REFERENCES

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
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.
Pro B, Advani R, Brice P, et al. Five-year results of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma. Blood 2017;130:2709-2717.

Brentuximab vedotin + bendamustine
Aubrais R, Bouabdallah K, Chartier L, et al. Salvage therapy with brentuximab-vedotin and bendamustine for patients with R/R PTCL: a retrospective study from the LYSA group. Blood Adv 2023;7:5733-5742.

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.
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.

DHAP (dexamethasone, cytarabine, and cisplatin) + platinum (carboplatin, cisplatin or oxaliplatin)
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.
Rigacci L, Fabbri A, Puccini B, et al. Oxaliplatin-based chemotherapy (dexamethasone, high-dose cytarabine, and oxaliplatin) ± rituximab is an effective salvage regimen in patients with relapsed or refractory lymphoma. Cancer 2010;116:4573-4579.
Tixier F, Ranchon F, Iltis A, et al. Comparative toxicities of 3 platinum-containing chemotherapy regimens in relapsed/refractory lymphoma patients. Hematol Oncol 2017;35:584-590.
Tessoulin B, Thomare P, Delande E, et al. Carboplatin instead of cisplatin in combination with dexamethasone, high-dose cytarabine with or without rituximab (DHAC+/-R) is an effective treatment with low toxicity in Hodgkin's and non-Hodgkin's lymphomas. Ann Hematol 2017;96:943-950.

Duvelisib
Brammer J, Zinzani P, Zain J, et al. Duvelisib in patients with relapsed/refractory peripheral T-cell lymphoma from the phase 2 Primo trial: Results of an interim analysis [abstract]. Blood 2021:138(Suppl 1): Abstract 2456.

ESHAP (etoposide, methylprednisolone, and cytarabine) + platinum (cisplatin or oxaliplatin)
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.
Sym SJ, Lee DH, Kang HJ, et al. A multicenter phase II trial of etoposide, methylprednisolone, high-dose cytarabine, and oxaliplatin for patients with primary refractory/relapsed aggressive non-Hodgkin's lymphoma. Cancer Chemother Pharmacol 2009;64:27-33.
Won YW, Lee H, Eom HS, et al. A phase II study of etoposide, methylprednisolone, high-dose cytarabine, and oxaliplatin (ESHAOx) for patients with refractory or relapsed Hodgkin's lymphoma. Ann Hematol 2020;99:255-264.

Gemcitabine
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.

GDP (gemcitabine, dexamethasone, and cisplatin)
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.
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.

GVD (gemcitabine, vinorelbine, and 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, and etoposide)
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.

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.

Ruxolitinib
Moskowitz AJ, Ghione P, Jacobsen E, et al. A phase 2 biomarker-driven study of ruxolitinib demonstrates effectiveness of JAK/STAT targeting in T-cell lymphomas. Blood 2021;138:2828-2837.

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

OVERVIEW OF BREAST IMPLANT-ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA (BIA-ALCL)

Definition

- **BIA-ALCL is an uncommon and emerging PTCL most frequently arising around a textured surface breast implant or in a patient with a history of a textured surface device.[a]**
- **BIA-ALCL commonly presents with delayed periprosthetic effusion and breast asymmetry occurring greater than 1 year (average, 7–9 years) after implantation. See Clinical Presentation (BIAA-1). Rarely, BIA-ALCL can present with a mass, regional lymphadenopathy, overlying skin rash, and/or capsular contracture.**
- **The majority of patients with BIA-ALCL exhibit an indolent clinical course with slow progression of disease and an excellent prognosis.**
- **Regional lymph node metastasis and more rarely distant organ and bone marrow metastasis may be seen in advanced stages.[b]**

Diagnosis

- **Tumor cells are CD30+, ALK-, have large anaplastic morphology on cytology, and demonstrate a single T-cell clone.[c]**
- **The histopathologic findings of BIA-ALCL need to be correlated with a clinical presentation and history of a breast implant to achieve a definitive diagnosis.[d]**
- **Diagnosis from effusions requires a sufficient volume of fluid (minimum, 50 mL) to achieve diagnosis. Prior serial aspirations may decrease or dilute tumor burden and make diagnosis more challenging; therefore, pathology review of the first aspiration is advisable.**
- **Multiple systematic sampling of scar capsulectomy specimen may be necessary to determine early invasive disease and mass formation, which have implications for prognosis.[e]**
- **Secondary review by a tertiary referral center is recommended for equivocal pathology.**

GENERAL PRINCIPLES OF BIA-ALCL

- **A multidisciplinary team approach involving lymphoma oncology, surgical oncology, hematopathology, and plastic surgery is often optimal for the treatment of patients with BIA-ALCL, particularly those with advanced disease.**
- **Given the rarity of the disease, the FDA recommends reporting cases to national disease registries to track cases (www.thepsf.org/PROFILE).**
- **Goals of therapy should be individualized but often include the following:**
  - **Generally, complete surgical resection alone of the implant, capsule, and associated mass is used in earlier stage disease confined to the periprosthetic scar capsule.[f]**
  - **May consider immediate or delayed breast reconstruction with autologous tissue or smooth surface breast implants.[g]**
  - **Local disease relapse may be amenable to re-excision surgery alone without requiring systemic therapies.**

[a] Mehta-Shah N, Clemens MW, Horwitz SM. How I treat breast implant-associated anaplastic large cell lymphoma. Blood 2018;132:1889-1898.

[b] Collins MS, Miranda RN, Medeiros LJ, et al. Characteristics and treatment of advanced breast implant-associated anaplastic large cell lymphoma. Plast Reconstr Surg 2019;143:41S-50S.

[c] Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia 2022;36:1720-1748; Campo E, Jaffe ES, Cook JR, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee. Blood 2022;140:1229-1253.

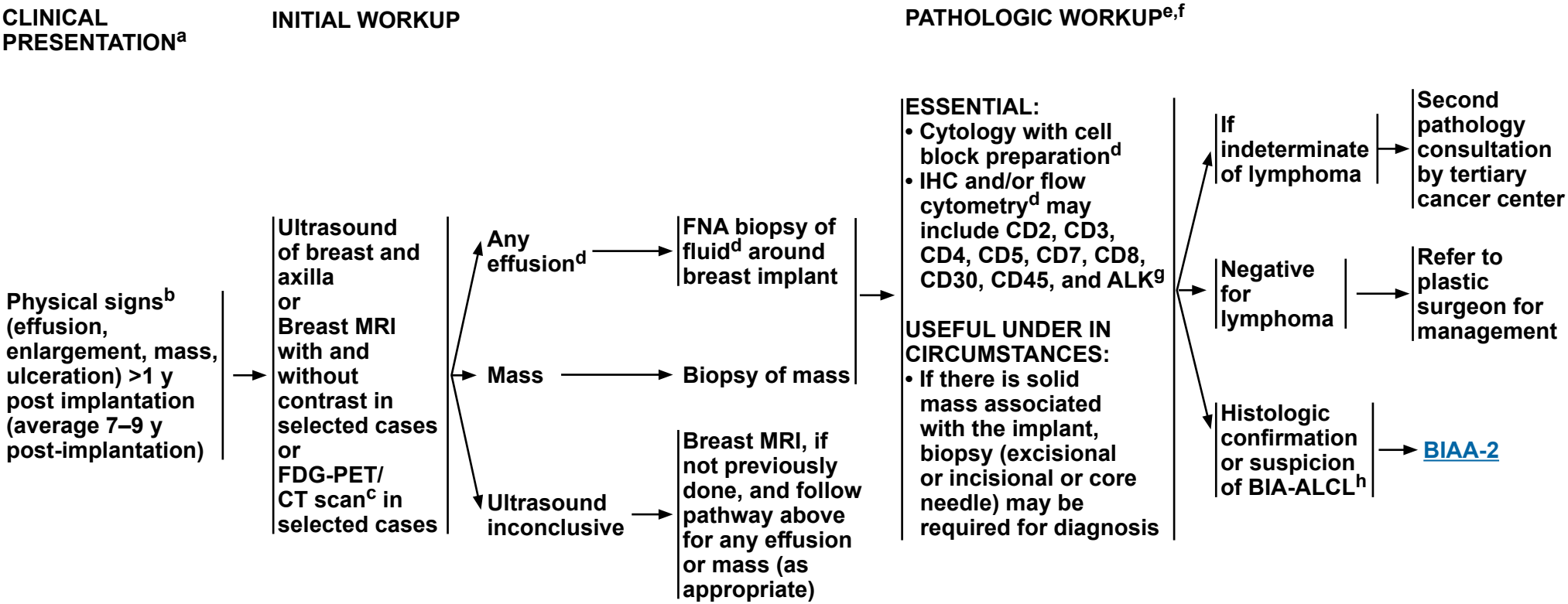
[d] Quesada AE, Medeiros LJ, Clemens MW, et al. Breast implant-associated anaplastic large cell lymphoma: A review. Mod Pathol 2019;32:166-188.

[e] Lyapichev KA, Pina-Oviedo S, Medieros LJ, et al. A proposal for pathologic processing of breast implant capsules in patients with suspected breast implant anaplastic large cell lymphoma. Mod Pathol 2020;33:367-379.

[f] 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.

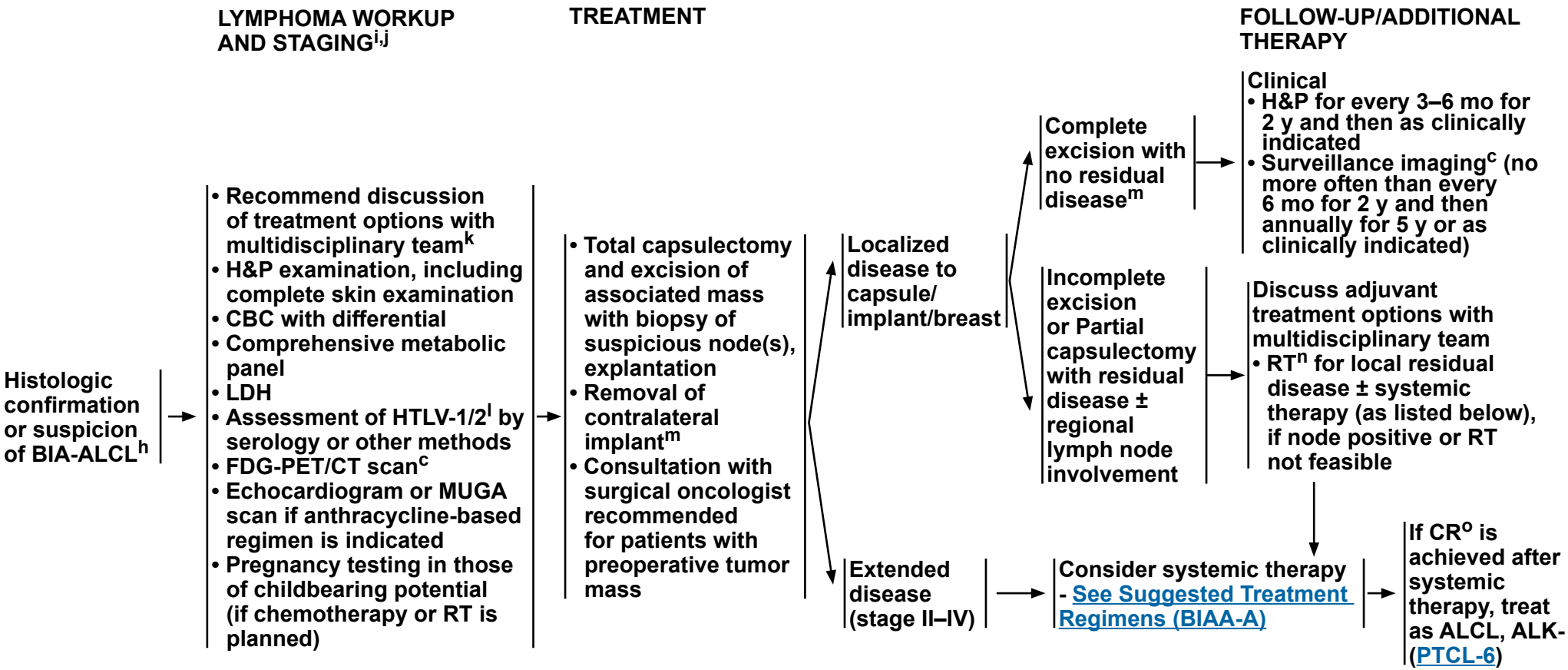
[g] Lamaris GA, Butler CE, Deva AK, et al. Breast reconstruction following breast implant-associated anaplastic large cell lymphoma. Plast Reconstr Surg 2019;143:51S-58S.

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



[a] Rare cases with parenchymal breast or nodal involvement may have an aggressive course more in line with systemic ALK-positive ALCL (PTCL-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] Patients with T-cell lymphomas often have extranodal disease, which may be inadequately imaged by CT. PET scan may be preferred in these instances.
[d] Larger volume of fluid yields a more accurate diagnosis. If possible, obtain >50 mL for cytology and cell block; >10 mL for flow cytometry immunophenotype.
[e] Principles of Molecular Analysis in T-Cell Lymphomas (TCLYM-A).
[f] Jaffe E, et al. J Clin Oncol 2020;38:1102-1111.
[g] BIA-ALCL is usually ALK-negative but has a good prognosis.
[h] The FDA recommends reporting all BIA-ALCL cases to the PROFILE Registry: www.thepsf.org/PROFILE.

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



[c] Patients with T-cell lymphomas often have extranodal disease, which may be inadequately imaged by CT. PET scan may be preferred in these instances.
[h] The FDA recommends reporting all BIA-ALCL cases to the PROFILE Registry: www.thepsf.org/PROFILE.
[i] Proposed TNM Staging for Breast Implant–Associated Anaplastic Large-Cell Lymphoma (BIAA-B).
[j] Bone marrow biopsy is only needed in selected cases (eg, extensive disease or unexplained cytopenia).
[k] Eg, medical oncologist/hematologist, surgical oncologist, plastic surgeon, hematopathologist.
[l] See map for prevalence of HTLV-1/2 by geographic region. HTLV-1/2 has been described in patients in non-endemic areas.
[m] In approximately 4.6% of cases, lymphoma was found in the contralateral breast (Clemens MW, et al. J Clin Oncol 2016;34:160-168).
[n] Principles of Radiation Therapy (TCLYM-D).
[o] Lugano Response Criteria for Non-Hodgkin Lymphoma (TCLYM-C).

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

SUGGESTED TREATMENT REGIMENS
(alphabetical order)

SYSTEMIC THERAPY

Preferred regimens
- **Brentuximab vedotin[a,b]**
- **Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone)[b]**

Other recommended regimens
- **CHOP**
- **CHOEP[c]**
- **Dose-adjusted EPOCH**

References

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.

Pro B, Advani R, Brice P, et al. Five-year results of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma. Blood 2017;130:2709-2717.

Horwitz S, O'Connor OA, Pro B, et al. The ECHELON-2 Trial: 5-year results of a randomized, phase III study of brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma. Ann Oncol 2022;33:288-298.

Footnotes

[a] Brentuximab vedotin may be appropriate for low-burden disease in selected patients.

[b] Supportive Care (TCLYM-B).

[c] Oral etoposide dose of 200 mg/m^2 (PO dosing of etoposide is 2 x the IV dose) may be substituted on days 2 and 3 for IV etoposide. Consider splitting the daily doses of oral etoposide over 200 mg.

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

Proposed TNM Staging for Breast Implant–Associated Anaplastic Large-Cell Lymphoma[1,2]

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	T any N any M1

[1] 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.

[2] Bilateral breast implantation for ALCL is not considered in this staging system. Complete excision of bilateral disease may be recommended if it is determined that 2 independent primaries are present (one on each side). Pathologic staging should be assessed in both sides. Identification of clonal abnormalities in bilateral cases is desirable and may help in determining if the disease represents metastasis.

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

OVERVIEW AND DEFINITION OF T-CELL LARGE GRANULAR LYMPHOCYTIC LEUKEMIA (LGLL)

- **LGLL is an indolent T-cell lymphoproliferative disorder (LPD) of the mature cytotoxic lymphocytes of effector memory cell phenotype. Most cases have an indolent and non-progressive clinical course, and moderate to severe autoimmune neutropenia is a frequent laboratory abnormality. Thrombocytopenia and anemia are less common and may accompany neutropenia leading to bilineage or trilineage cytopenias.**
- **There is significant clinical and pathophysiologic overlap with autoimmune syndromes, and in the majority of patients, LGLL is diagnosed concurrently with rheumatologic disease (ie, rheumatoid arthritis [RA] and systemic lupus erythematosus [SLE]) suggesting immunogenetic polymorphism is a mutual origin. Persistent large granular lymphocytosis (LGL) can also accompany other chronic autoimmune conditions such as Crohn's disease, Sjogren's syndrome, and psoriatic arthritis. It is therefore unclear, especially in patients with indolent non-progressive clinical course, whether the disease represents true malignant process or persistent maladaptive autoimmune response to autoantigens on hematopoietic elements with resultant autoimmune cytopenias.**
- **The diagnosis is generally established based on the persistence (>6 months) of LGL with typical morphologic features (moderate to copious cytoplasm with prominent azurophilic granules) in the peripheral blood and the bone marrow of the patients (>2000/uL), and exclusion of other potential conditions or illnesses where LGL is part of the pathologic process (ie, viral infections, other malignancies, rheumatologic disease). Mild splenomegaly is common, but significant splenic enlargement should trigger investigation of other etiologies. The degree of blood and bone marrow involvement do not necessarily correlate with disease severity or the grade of cytopenias.**
- **The TCR clonality studies may demonstrate oligoclonal or monoclonal pattern that does not correlate with disease aggressiveness. T-cell LGLLs (T-LGLLs) frequently demonstrate normal antigenic profile and express CD2, CD3, CD8, CD57, and TCRαß; in most cases, cells express cytotoxic markers TIA1, granzyme B, and granzyme M. In rare cases, LGLLs are CD4+ alpha-beta T cells or gamma-delta T cells (CD8+ or CD4-/CD8-).**
- **Characteristic genetic features found in approximately 30% of LGLL cases are activating somatic *STAT3* mutations affecting the *SH2* domain; the majority of the mutations are heterozygous. *STAT5B* SH2 mutations have also been reported.**
- **Main differential diagnosis includes HSTCL, aggressive NK-cell leukemia (ANKL) (ENKL-C), EBV-positive T-cell and NK-cell lymphoproliferative diseases of childhood, and reactive gamma-delta T-cell proliferations.**

Diagnosis and Workup (LGLL-1)

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

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DIAGNOSIS[a,b]

ESSENTIAL:[c,d]
- **Peripheral blood smear analysis for cytology; presence of large granular lymphocytes characterized by reniform or round nucleus and abundant cytoplasm containing azurophilic granules**
- **Peripheral blood flow cytometry with adequate immunophenotyping to establish diagnosis[e]**
  - **Cell surface marker analysis by flow cytometry may include: CD3, CD4, CD5, CD7, CD8, CD56, CD57, TCRαß, TCRγδ**

USEFUL IN CERTAIN CIRCUMSTANCES:
- **Bone marrow aspirate and biopsy[f]**
  - **IHC panel may include: CD3, CD4, CD5, CD7, CD8, CD56, CD57, TCRβ, TCRɣ, TIA1, perforin, granzyme B**
- **Mutational analysis: *STAT3* and *STAT5B***
- **Molecular analysis to detect clonal *TCR* gene rearrangements or other assessment of clonality[g]**
- **EBER-ISH**

→

WORKUP

ESSENTIAL:
- **H&P examination: Evaluation of enlarged spleen, liver; presence of lymphadenopathy (rare)**
- **Presence of autoimmune disease[c] (especially RA and SLE)**
- **Performance status**
- **CBC with differential**
- **Comprehensive metabolic panel**
- **Pregnancy testing in those of childbearing potential (if chemotherapy or RT is planned)**

USEFUL IN CERTAIN CIRCUMSTANCES
- **Serological markers for autoimmune disease[c]**
- **HIV testing**
- **Hepatitis B and C testing**
- **CMV serology if therapy with alemtuzumab is contemplated**
- **Consider quantitative EBV PCR**
- **Assessment of HTLV-1/2[h] by serology or other methods**
- **Ultrasound of liver/spleen**
- **C/A/P CT with contrast of diagnostic quality**
- **Echocardiogram[i]**
- **Discuss fertility preservation[j]**

→ **Indication for Treatment (LGLL-2)**

[a] Approximately 10% of LGLL cases will be of the NK-cell subtype (chronic LPD of NK cells [ICC]; NK-large granular lymphocytic leukemia [WHO5]). These are treated with a similar approach to T-LGLL.

[b] Principles of Molecular Analysis in T-Cell Lymphomas (TCLYM-A).

[c] Autoimmune disorders (especially RA and SLE) can occur in patients with T-LGLL. Small, clinically non-significant clones of T-LGLLs can be detected concurrently in patients with bone marrow failure disorders.

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

[e] Typical immunophenotype for T-LGLL: CD3+, CD8+, CD16+, CD57+, CD56+/-, CD28, CD5 dim, and/or CD7 dim, CD45RA+, CD62L-, TCRαβ+, TIA1+, granzyme B+, or granzyme M+. Overlap with reactive LGL is frequent.

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

[g] Clonal *TCR* gene rearrangements alone are not sufficient for diagnosis, as these can also be seen in patients with non-malignant conditions. Results should be interpreted in the context of overall presentation. See Principles of Molecular Analysis in T-Cell Lymphomas (TCLYM-A).

[h] See map for prevalence of HTLV-1/2 by geographic region. HTLV-1/2 has been described in patients in non-endemic areas.

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

[j] Fertility preservation options include: sperm banking, semen cryopreservation, IVF, or ovarian tissue or oocyte cryopreservation.

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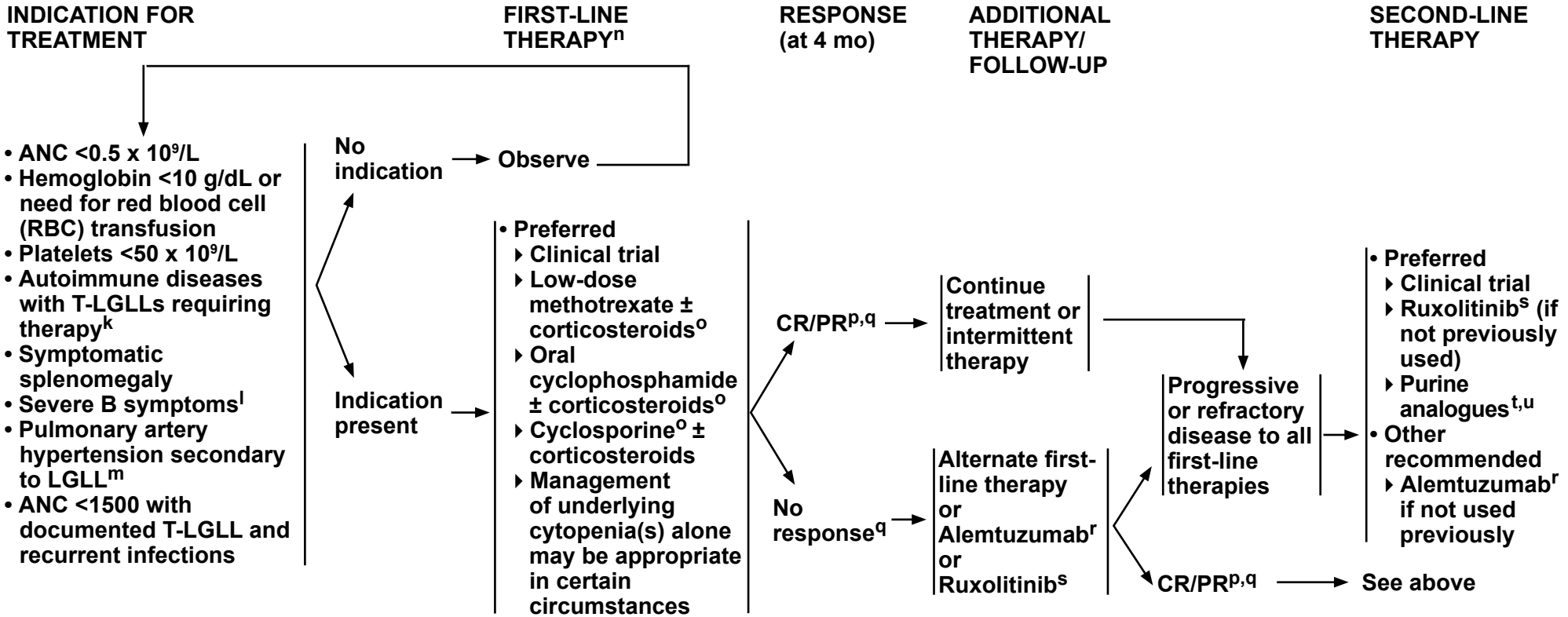

[k] Treat underlying autoimmune disease.
[l] Exclude underlying associated malignancy, viral syndrome, or autoimmune disease.
[m] Grossi O, et al. Euro Respir J 2012;39:493-494.
[n] Monitoring for cumulative toxicity is recommended for long-term use with methotrexate.
[o] Methotrexate with or without 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, et al. Blood 2011;117:2764-2774; Braunstein Z, et al. Blood Adv 2022;6:2685-2687).
[p] CR 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 LGLL counts within normal range (<0.5 x 10^9/L). PR 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, et al. Hematologica 2010;95:1534-1541).
[q] Limit therapy with cyclophosphamide to 4 mo if no response and consider limiting to ≤12 mo if PR observed at 4 mo due to increased risk of bladder toxicity, mutagenesis, and leukemogenesis (Lamy T, et al. Blood 2011;117:2764-2774).
[r] While alemtuzumab is no longer commercially available, it may be obtained for clinical use. Low-dose alemtuzumab is typically used for LGLL (Dumitriu B, et al. Lancet Haematol 2016;3:e22-e29). CMV monitoring or prophylaxis is recommended (TCLYM-B).
[s] In the phase II studies, ruxolitinib was dosed at 20 mg BID. Due to the prevalence of cytopenias in patients with LGLL, dose reductions to 10 or 5 mg BID can be considered. Frequent CBC monitoring is recommended. (Moskowitz A, et al. Blood 2021;138:2828-2837; Moskowitz A, et al. Blood 2023;142:Abstract 183)
[t] Supportive Care (TCLYM-B).
[u] Pentostatin, cladribine, and fludarabine have been used in LGLL.

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

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DIAGNOSIS[a,b]

ESSENTIAL:
- Tissue histology not essential for diagnosis
- Peripheral blood smear analysis for morphology
- Peripheral blood flow cytometry with adequate immunophenotyping to establish diagnosis[c]
  - Cell surface marker analysis may include: TdT, CD1a, CD2, CD3, CD4, CD5, CD7, CD8, CD52, TCRαβ, TCL1
- Cytogenetics (fluoresence in situ hybridization [FISH] and karyotype): inv(14)(q11;q32); t(14;14)(q11;q32); t(X;14)(q28;q11); trisomy 8

USEFUL IN CERTAIN CIRCUMSTANCES:
- Molecular analysis to detect clonal *TCR* gene rearrangements or other assessment of clonality[d]
- Bone marrow aspirate and biopsy
  - IHC panel may include: CD1a, TdT, CD2, CD3, CD5, TCL1

WORKUP

ESSENTIAL:
- H&P examination, including complete skin examination, and evaluation of lymph nodes, spleen, and liver
- Performance status
- LDH
- CBC with differential
- Comprehensive metabolic panel
- Assessment of HTLV-1/2[e] by serology or other methods
- FDG-PET/CT scan[f] and/or C/A/P CT with contrast
- Pregnancy testing in those of childbearing potential (if chemotherapy or RT is planned)

USEFUL IN CERTAIN CIRCUMSTANCES
- Echocardiogram or MUGA scan if treatment includes regimens containing anthracyclines or anthracenediones
- Bone marrow evaluation
- HIV testing
- Hepatitis B and C testing
- Consider screening for active infections and cytomegalovirus (CMV) serology if therapy with alemtuzumab is contemplated
- Human leukocyte antigen (HLA) typing
- Discuss fertility preservation[g]

Asymptomatic disease[h] → Observe until progression or symptomatic

Symptomatic disease → TPLL-2

[a] Diagnostic Criteria for TPLL (TPLL-A).
[b] Principles of Molecular Analysis in T-Cell Lymphomas (TCLYM-A).
[c] Typical immunophenotype: CD1a-, TdT-, CD2+, sCD3+/-, cCD3+/-, CD5+, CD7++, CD52++, TCRαß+, CD4+/CD8- (65%), CD4+/CD8+ (21%), CD4-/CD8+ (13%).
[d] Clonal *TCR* gene rearrangements alone are not sufficient for diagnosis, as these can also be seen in patients with non-malignant conditions. Results should be interpreted in the context of overall presentation. See Principles of Molecular Analysis in T-Cell Lymphomas (TCLYM-A).
[e] See map for prevalence of HTLV-1/2 by geographic region. HTLV-1/2 has been described in patients in non-endemic areas.
[f] Patients with T-cell lymphomas often have extranodal disease, which may be inadequately imaged by CT. PET scan may be preferred in these instances.
[g] Fertility preservation options include: sperm banking, semen cryopreservation, IVF, or ovarian tissue or oocyte cryopreservation.
[h] 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.

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

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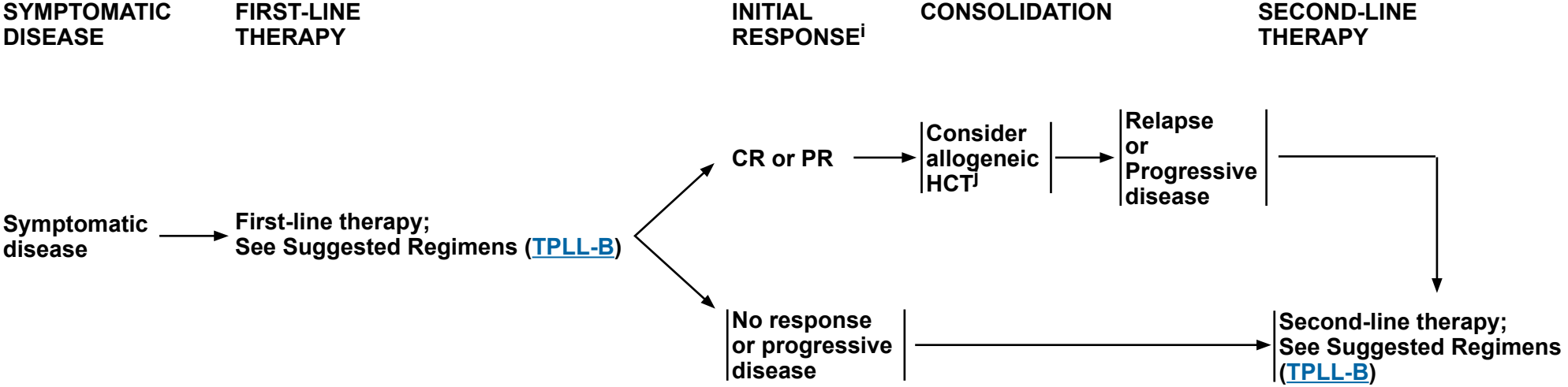


[i] Response Criteria for TPLL (TPLL-C).
[j] Consider autologous HCT, if a suitable donor is not available.

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

DIAGNOSTIC CRITERIA FOR T-CELL PROLYMPHOCYTIC LEUKEMIA (T-PLL)[a]

- **The diagnosis of T-PLL is established if all 3 major criteria are met or if the first 2 major criteria and 1 minor criterion are met.**

Major Criteria	Minor Criteria (at least 1 required)
• >5 x10^9/L cells of T-PLL phenotype in peripheral blood or bone marrow	• Abnormalities involving chromosome 11 (11q22.3; *ATM*)
• T-cell clonality (by PCR for *TRB*/*TRG*, or by flow cytometry)	• Abnormalities in chromosome 8: idic(8)(p11), t(8;8), trisomy 8q
• Abnormalities of 14q32 or Xq28 OR expression of *TCL1A/B*, or *MTCP1**	• Abnormalities in chromosomes 5, 12, 13, 22, or complex karyotype
	• Involvement of T-PLL–specific site (eg, splenomegaly, effusions)

*Cases without *TCL1A*, *TCL1B*, or *MTCP1* rearrangement or their respective overexpression are collected as TCL1-family negative T-PLL.

[a] Staber P, Herling M, Bellido M, et al. Consensus criteria for diagnosis, staging, and treatment response assessment of T-cell prolymphocytic leukemia. Blood 2019;134:1132-1143.

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

SUGGESTED TREATMENT REGIMENS[a,b]

FIRST-LINE THERAPY

Preferred regimens
- Clinical trial
- Alemtuzumab (IV) alone[c,d]

Other recommended regimens[c,d]
- FMC (fludarabine, mitoxantrone, cyclophosphamide) followed by alemtuzumab (IV) in selected patients
- Alemtuzumab (IV) and pentostatin in selected patients

SECOND-LINE THERAPY OR SUBSEQUENT THERAPY

Preferred regimens
- Clinical trial
- Pentostatin

Other recommended regimens
- Alternate regimens not used in first-line therapy
- Ruxolitinib

Useful in certain circumstances
- Retreatment with alemtuzumab[d] (IV) ± pentostatin (if CD52 expression is still positive and relapse after a period of remission following first-line therapy)

[a] See references for regimens on TPLL-B 2 of 2.
[b] Consider prophylaxis for TLS (TCLYM-B).
[c] IV infusion is preferred over SC delivery based on data showing inferior activity with SC delivery in patients with T-PLL (Dearden CE, et al. Blood 2011;118:5799-5802).
[d] While alemtuzumab is no longer commercially available, it may be obtained for clinical use. CMV monitoring or prophylaxis is recommended (TCLYM-B).

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

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.

Pentostatin

Döhner H, Ho AD, Thaler J, et al. Pentostatin in prolymphocytic leukemia: phase II trial of the European Organization for Research and Treatment of Cancer Leukemia Cooperative Study Group. J Natl Cancer Inst 1993;85:658-662.

Ruxolitinib

Moskowitz AJ, Ghione P, Jacobsen E, et al. A phase 2 biomarker-driven study of ruxolitinib demonstrates effectiveness of JAK/STAT targeting in T-cell lymphomas. Blood 2021;138:2828-2837.

Allogeneic HCT

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;26:972-976.

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.

RESPONSE CRITERIA FOR T-PLL[a]

Group and Parameter	CR (all met)	PR (≥2 in A and ≥1 in B)	SD (all met)	PD (≥1 in A or B met)
Group A				
Lymph nodes	Long-axis diameters to <1.0 cm	Decrease ≥30% in SLD	Change of – <30% to + ≤20%	Increase >20% in SLD
Spleen size	Spleen size <13 cm	Decrease ≥50% in vertical length beyond normal from baseline	Change of –49% to +49% beyond normal from baseline	Increase ≥50% in vertical length beyond normal from baseline
Constitutional symptoms	None	Any	Any	Any
Circulating lymphocyte count	<4 x 10^9/L	≤30 x 10^9/L and decrease ≥50% from baseline	>30 x 10^9/L or change of –49% to +49%	Increase ≥50% from baseline
Marrow	T-PLL cells <5% of mononuclear cells	Any	Any	Any
Any other specific site involvement*	None	Any	Any	Any
Group B				
Platelet count	≥100 x 10^9/L	≥100 x 10^9/L or increase ≥50% from baseline	Change of –49% to +49%	Decrease ≥50% over baseline
Hemoglobin	≥11.0 g/dL (untransfused)	≥11 g/dL or increase ≥50% from baseline	11.0 g/dL or <50% from baseline, or change <2 g/dL	Decrease of ≥2 g/dL from baseline
Neutrophils	≥1.5 x 10^9/L	≥1.5 x 10^9/L or increase ≥50% from baseline	Change of –49% to +49%	Decrease of ≥50% from baseline

CR, all of the criteria have to be met; CRi, all CR criteria of group A are met but at least 1 in B is not achieved;
PR, at least 2 parameters of group A and 1 of group B need to improve if previously abnormal;
PD, at least 1 of the criteria of group A or group B has to be met; SD, all the criteria have to be met, constitutional symptoms alone do not define PD;
SLD, sum of long-axis diameters of up to 3 target lesions.
*Pleural or peritoneal effusion, skin infiltration, or CNS involvement.

[a] Staber P, Herling M, Bellido M, et al. Consensus criteria for diagnosis, staging, and treatment response assessment of T-cell prolymphocytic leukemia. Blood 2019;134:1132-1143.

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

DIAGNOSIS[a]

ESSENTIAL[b]:

- **CBC with differential and peripheral blood smear for atypical cells[c]: lymphocytosis (ALC >4000/μL in adults) in acute and chronic subtypes[d]**
- **Peripheral blood flow cytometry with adequate immunophenotyping to establish diagnosis[e]**
- **Cell surface marker analysis by flow cytometry may include: CD2, CD3, CD4, CD5, CD7, CD8, CD25, CD30, TCRαß**
- **Assessment of HTLV-1/2 by serology or other methods[f]**

USEFUL IN CERTAIN CIRCUMSTANCES:

- **Biopsy of lymph nodes (excisional), skin biopsy, GI tract, or bone marrow biopsy[g] 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 IHC is as follows[e,h,i]: CD3, CD4, CD5, CD7, CD8, CD25, CD30**
- **Cell surface marker analysis by flow cytometry for CCR4**
- **Consider NGS panel**

→

WORKUP

ESSENTIAL:

- **H&P examination, including complete skin examination**
- **Comprehensive metabolic panel**
- **LDH**
- **Serology for strongyloides**
- **FDG-PET/CT scan[j] ± C/A/P/neck CT with contrast**
- **Pregnancy testing in those of childbearing potential (if chemotherapy or RT is planned)**

USEFUL IN CERTAIN CIRCUMSTANCES:

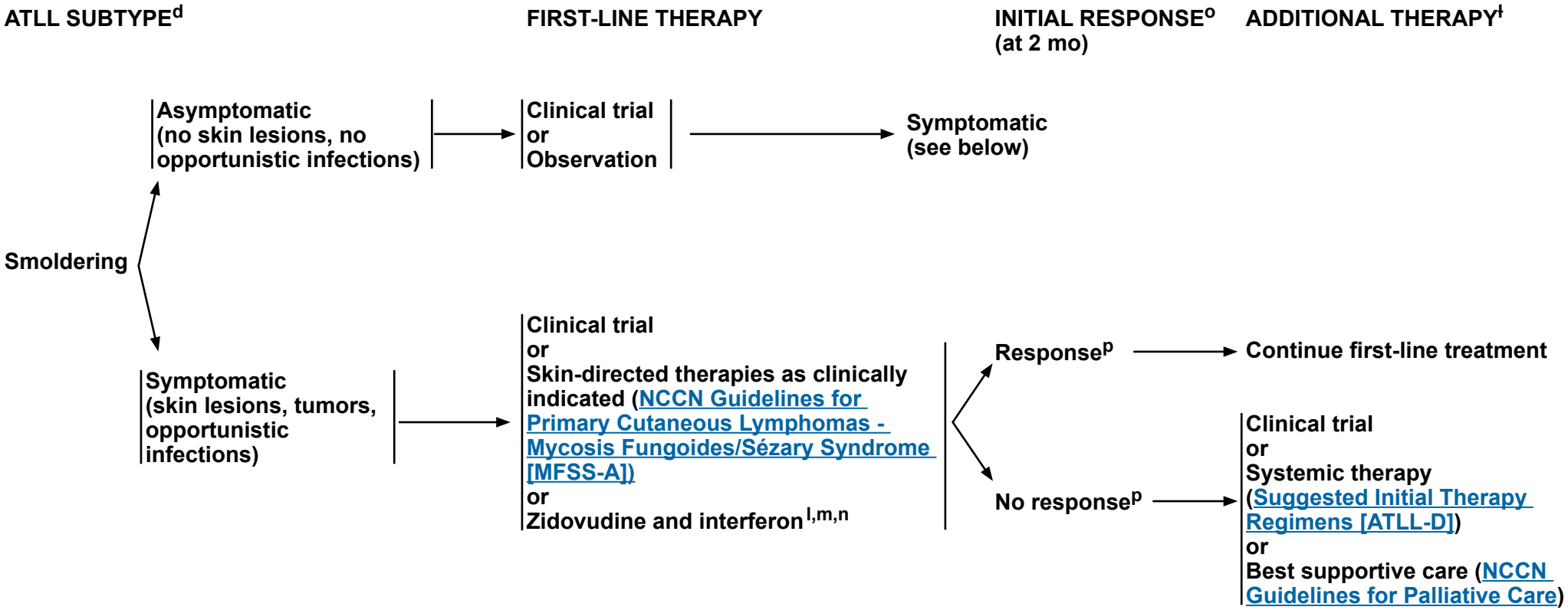
- **HIV testing**
- **Hepatitis B and C testing**
- **CRP, soluble interleukin-2 receptor (sIL-2R), serum albumin, and blood urea nitrogen (BUN)**
- **Upper gastrointestinal endoscopy**
- **Echocardiogram or MUGA scan if anthracycline-based regimen is indicated**
- **CNS evaluation: Head CT or MRI with contrast and/or lumbar puncture in all patients with acute or lymphoma subtypes or in patients with neurologic manifestations**
- **Uric acid**
- **HLA typing**
- **Discuss fertility preservation[k]**

ATLL SUBTYPE[d]

- **Smoldering subtype (ATLL-2)**
- **Chronic subtype (ATLL-3)**
- **Acute subtype (ATLL-4)**
- **Lymphoma subtype (ATLL-4)**

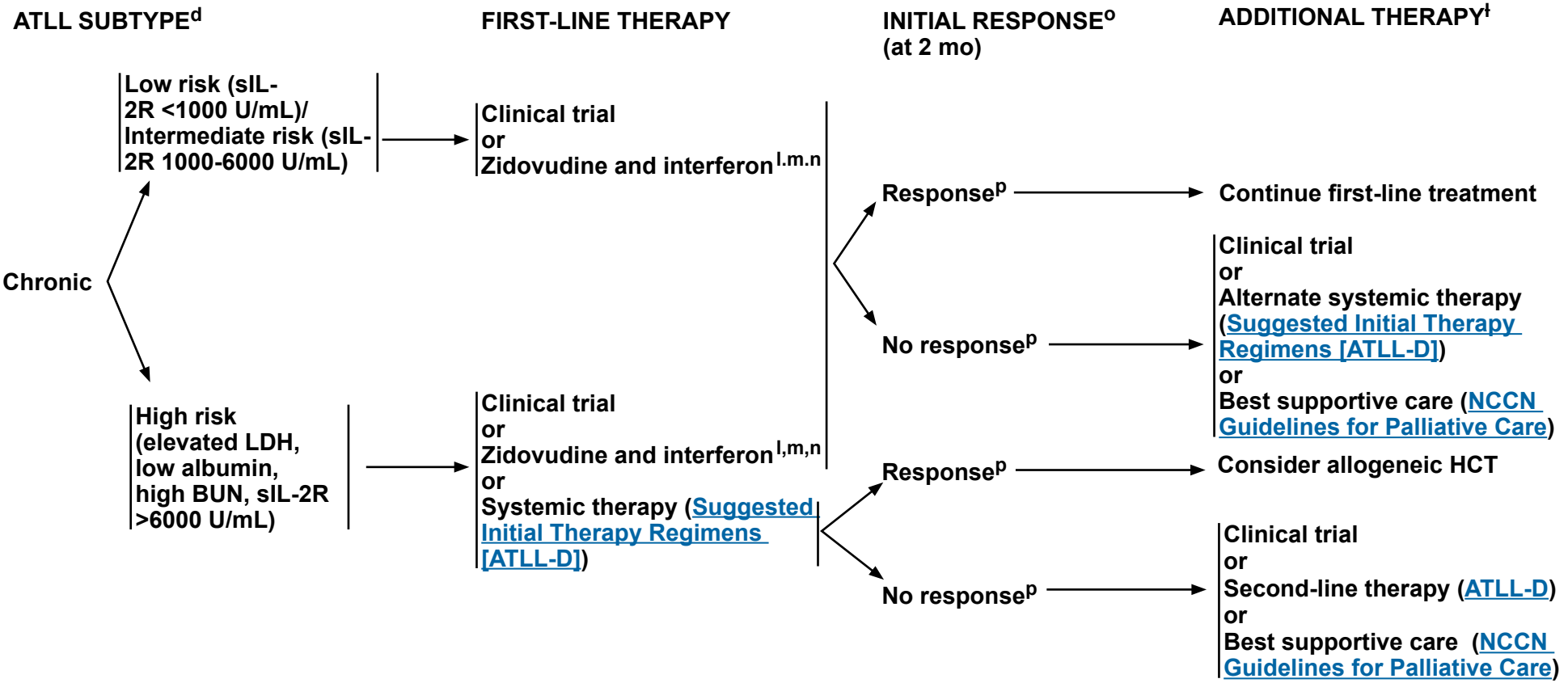
[a] Principles of Molecular Analysis in T-Cell Lymphomas (TCLYM-A).
[b] The diagnosis of ATLL requires peripheral blood cytology or tissue histopathology and immunophenotyping of tumor lesion, or morphology and immunophenotyping of peripheral blood *and* HTLV-1 serology.
[c] Typical ATLL cells ("flower 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 of blood involvement in the absence of other criteria.
[d] Diagnostic Criteria for ATLL (ATLL-A).
[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] See map for prevalence of HTLV-1/2 by geographic region. HTLV-1/2 has been described in patients in non-endemic areas.
[g] Bone marrow involvement is an independent poor prognostic factor.
[h] Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (TCLYM-E).
[i] 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.
[j] Patients with T-cell lymphomas often have extranodal disease, which may be inadequately imaged by CT. PET scan may be preferred in these instances.
[k] Fertility preservation options include: sperm banking, semen cryopreservation, IVF, or ovarian tissue or oocyte cryopreservation.

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



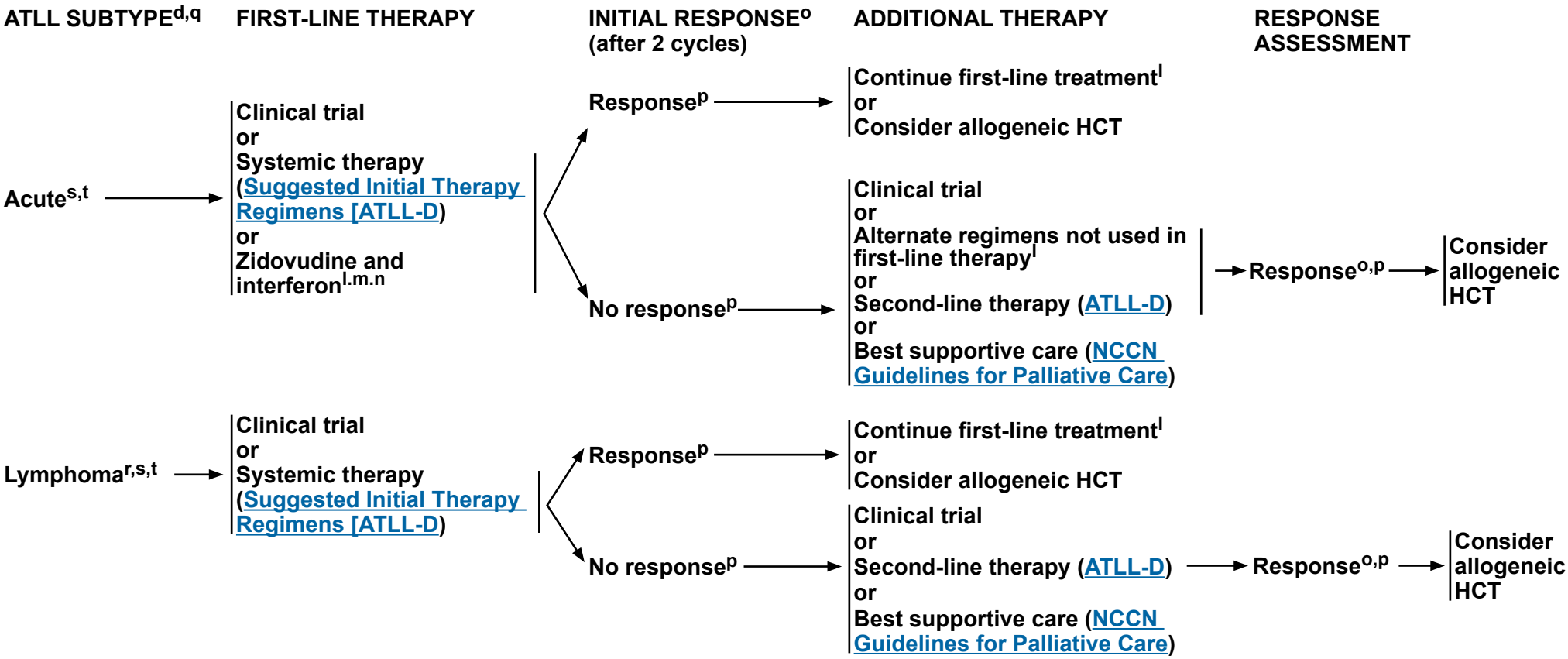
[d] Diagnostic Criteria for ATLL (ATLL-A).
[l] Outside of a clinical trial, if the disease is not responding or is progressing, treatment with zidovudine and interferon should be stopped. If there is evidence of clinical benefit, treatment should continue until best response is achieved. If life-threatening manifestations, treatment can be discontinued before the 2-month period.
[m] See references for zidovudine and interferon (ATLL-D 2 of 2).
[n] Peginterferon alfa-2a is the only alpha interferon available for clinical use in the United States and it may be substituted for other alpha interferon preparations (Schiller M, et al. J Eur Acad Dermatol Venerol 2017;31:1841-1847; Patsatsi A, et al. J Eur Acad Dermatol Venereol 2022;36:e291-e293; Osman S, et al. Dermatologic Therapy 2023;2023:7171937).
[o] If nodal disease is present, repeat C/A/P CT with contrast or FDG-PET/CT.
[p] See Response Criteria for ATLL (ATLL-B). Responders include CR, uncertified CR, and PR.

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



[d] Diagnostic Criteria for ATLL (ATLL-A).
[l] 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.
[m] See references for zidovudine and interferon (ATLL-D 2 of 2).
[n] Peginterferon alfa-2a is the only alpha interferon available for clinical use in the United States and it may be substituted for other alpha interferon preparations (Schiller M, et al. J Eur Acad Dermatol Venerol 2017;31:1841-1847; Patsatsi A, et al. J Eur Acad Dermatol Venereol 2022;36:e291-e293; Osman S, et al. Dermatologic Therapy 2023;2023:7171937).
[o] If nodal disease is present, repeat C/A/P CT with contrast or FDG-PET/CT.
[p] See Response Criteria for ATLL (ATLL-B). Responses include CR, uncertified CR, and PR.

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



[d] Diagnostic Criteria for ATLL (ATLL-A).
[l] Outside of a clinical trial, if the disease is not responding or is progressing within a 2-month period, 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.
[m] See references for zidovudine and interferon (ATLL-D 2 of 2).
[n] Peginterferon alfa-2a is the only alpha interferon available for clinical use in the United States and it may be substituted for other alpha interferon preparations (Schiller M, et al. J Eur Acad Dermatol Venerol 2017;31:1841-1847; Patsatsi A, et al. J Eur Acad Dermatol Venereol 2022;36:e291-e293; Osman S, et al. Dermatologic Therapy 2023;2023:7171937).
[o] If nodal disease is present, repeat C/A/P CT with contrast or FDG-PET/CT.
[p] See Response Criteria for ATLL (ATLL-B). Responses include CR, uncertified CR, and PR.
[q] Modified Prognostic Index for Aggressive ATLL (ATLL-C).
[r] The long-term efficacy of initial therapies alone is limited. Allogeneic HCT may be a curative option for some patients.
[s] CNS disease is common and prophylaxis is recommended.
[t] Antiviral therapy is not effective.

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

DIAGNOSTIC CRITERIA FOR ATLL

	Smoldering	Chronic	Lymphoma	Acute
Anti-HTLV-1 antibody	+	+	+	+
Lymphocyte (x 10^9 /1/L)	<4	≥4[a]	<4	*
Abnormal T lymphocytes	≥5%	+[b]	≤1%	+[b]
Flower cells of T-cell marker	Occasionally	Occasionally	No	+
LDH	≤1.5N	≤2N	*	*
Corrected Ca (mmol/1/L)	<2.74	<2.74	*	*
Histology-proven lymphadenopathy	No	*	+	*
Tumor lesion				
Skin	**	*	*	*
Lung	**	*	*	*
Lymph node	No	*	Yes	*
Liver	No	*	*	*
Spleen	No	*	*	*
CNS	No	No	*	*
Bone	No	No	*	*
Ascites	No	No	*	*
Pleural effusion	No	No	*	*
GI tract	No	No	*	*

* No essential qualification except terms required for other subtype(s).
** No essential qualification if other terms are fulfilled, but histology-proven malignant lesion(s) is required in case abnormal T lymphocytes are less than 5% in peripheral blood.

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.

[a] Accompanied by T lymphocytosis (3.5 x 109/1 or more).
[b] In case abnormal T lymphocytes are less than 5% in peripheral blood, histology-proven tumor lesion is required.

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

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 x 10^9/L.
‡Calculated by the sum of the products of the greatest diameters of measurable disease.
§Defined by ≥50% increase from nadir in the sum of the products of measurable disease.
#Defined by ≥50% increase from nadir in the count of flower cells and an absolute lymphocyte count, including flower cells, of >4 x 10^9/L.

[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.

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

MODIFIED PROGNOSTIC INDEX FOR AGGRESSIVE ATLL[a]

RISK FACTORS	RISK GROUPS	
• Clinical subtype of acute ATLL	Low	0–1
• CRP level ≥2.5 mg/dL	Intermediate	2–3
• ECOG PS 2–4	High	4–5
• sIL-2R >5,000 U/mL		
• Adjusted Ca level ≥12 mg/dL		

[a] Used with permission of Fondazione Adolfo Ferrata ed Edoardo Storti from Fuji S, Yamaguchi T, Inoue Y, et al. Development of a modified prognostic index for patients with aggressive adult T-cell leukemia-lymphoma aged 70 years or younger: possible risk-adapted management strategies including allogeneic transplantation. Haematologica 2017;102:1258-1265.

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

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SUGGESTED TREATMENT REGIMENS[a,b]

INITIAL THERAPY

Preferred regimens (regimens in alphabetical order)
- Clinical trial
- Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone) for CD30+ cases
- Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin)
- Zidovudine and interferon[c] (acute, chronic, and symptomatic smoldering subtypes)

Other recommended regimens (alphabetical order)
- CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone)
- HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine

Useful in certain circumstances
- CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) (unable to tolerate intensive regimen or non-CD30 expressing ATLL)

SECOND-LINE THERAPY OR SUBSEQUENT THERAPY

Preferred regimens (regimens in alphabetical order)
- Clinical trial
- Single agents
  - Brentuximab vedotin for CD30+ cases
  - Lenalidomide[d]
  - Mogamulizumab[d,e]
- Combination regimens
  - DHA (dexamethasone and cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin)
  - ESHA (etoposide, methylprednisolone, and cytarabine) + platinum (cisplatin or oxaliplatin)
  - GDP (gemcitabine, dexamethasone, and cisplatin)
  - GemOx (gemcitabine and oxaliplatin)
  - GVD (gemcitabine, vinorelbine, and liposomal doxorubicin)
  - ICE (ifosfamide, carboplatin, and etoposide)
  - Zidovudine and interferon[c] (acute, chronic, and symptomatic smoldering subtypes)

Alternative regimens (alphabetical order)
- Single agents
  - Alemtuzumab[f]
  - Arsenic trioxide
  - Belinostat
  - Bendamustine
  - Bortezomib
  - Gemcitabine
  - Pralatrexate
  - RT in selected cases with localized, symptomatic disease[g]

[a] See ATLL-D 2 of 2) for references for regimens.
[b] See Supportive Care (TCLYM-B) for TLS prophylaxis and anti-infective prophylaxis.
[c] Peginterferon alfa-2a is the only alpha interferon available for clinical use in the United States and it may be substituted for other alpha interferon preparations (Schiller M, et al. J Eur Acad Dermatol Venerol 2017;31:1841-1847; Patsatsi A, et al. J Eur Acad Dermatol Venereol 2022;36:e291-e293; Osman S, et al. Dermatologic Therapy 2023;2023:7171937).
[d] Lenalidomide and mogamulizumab may be associated with higher incidences of graft-versus-host disease (GVHD) after allogeneic HCT.
[e] Higher responses have been observed in patients with leukemic disease. *CCR4* gain-of-function mutations have been reported to be predictive of sensitivity to mogamulizumab treatment (Sakamoto Y, et al. Blood 2018;132;758-761).
[f] While alemtuzumab is no longer commercially available, it may be obtained for clinical use. CMV monitoring or prophylaxis is recommended (TCLYM-B).
[g] Principles of Radiation Therapy (TCLYM-D).

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

REFERENCES

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, 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.
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.

Initial Therapy

Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone)
Horwitz S, O'Connor OA, Pro B, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. Lancet 2019;393:229-240.

CHOP
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.
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.

Dose-adjusted EPOCH
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.
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.

HyperCVAD
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.

Second-line Therapy or Subsequent Therapy

Alemtuzumab
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.

Arsenic trioxide
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.

Bortezomib
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.

Brentuximab vedotin
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.

Lenalidomide
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.

Mogamulizumab
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.
Phillips AA, Fields PA, Hermine O, et al. Mogamulizumab versus investigator's choice of chemotherapy regimen in relapsed/refractory adult T-cell leukemia/lymphoma. Haematologica 2019;104:993-1003.

Pralatrexate
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 [abstract]. Blood 2012;120:Abstract 2735.

See PTCL-B (8 of 8) for references for combination regimens.

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

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OVERVIEW AND DEFINITION OF HEPATOSPLENIC T-CELL LYMPHOMA (HSTCL)[a,b]

- **HSTCL is a rare, systemic, mature T-cell malignancy most often characterized by spleen, liver, and bone marrow involvement and an aggressive clinical course. Bulky lymphadenopathy is uncommon.**
- **The disease predominantly affects patients assigned male at birth with a median age of 35 years. Up to 20% of cases arise in chronic immune suppression. Patients frequently present with systemic symptoms, hepatosplenomegaly, cytopenias, and sometimes hemophagocytic lymphohistiocytosis (HLH).**
- **The diagnosis is most frequently reached by histologic examination of a bone marrow biopsy, and/or a liver biopsy or splenectomy. On bone marrow histology the neoplastic T cells may be difficult to identify, and IHC is required for the diagnosis.**
- **The neoplastic cells are cytotoxic T cells, frequently with surface expression of TCRγδ, and typically show the following phenotype: CD2+, CD3+, CD4-, CD5-, CD8-/+, CD56+/-, TIA1+, granzyme B-. A small subset express TCRαβ, which is described as a variant of HSTCL.**
- **A *TCRγ* gene rearrangement on molecular analysis reflects clonality of the T cell, but may be seen in alpha/beta or gamma/delta-expressing T cells and is NOT necessarily synonymous with a gamma/delta T-cell lymphoma.**
- **Characteristic genetic features include isochromosome 7q, trisomy 8, activating mutations of *JAK/STAT* pathway (ie, *STAT5B*, *STAT3*), and chromatin-modifying genes (ie, *SETD2*, *INO80*, *ARID1B*).[c]**
- **Main differential diagnosis includes gamma/delta-expressing T-LGLL, reactive gamma/delta T-cell proliferations, ANKL, EBV-positive T-cell and NK-cell lymphoproliferative diseases of childhood, and, rarely, other T-cell lymphomas that may have gamma/delta expression.**
- **Long-term remission is primarily or exclusively seen in those who have undergone consolidative HCT.**

Diagnosis (HSTCL-1)

[a] Krishnan M, Lunning M. Hepatosplenic γ-δ T-cell lymphoma: Who is on your speed dial? J Oncol Pract 2019;15:307-312.
[b] Pro B, Allen PB, Behdad A. Hepatosplenic T-cell lymphoma: A rare but challenging entity. Blood 2020;136:2018-2026.
[c] McKinney M, Moffitt AB, Gaulard P, et al. The genetic basis of hepatosplenic T-cell lymphoma. Cancer Discov 2017;7:369-379.

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

DIAGNOSIS[a,b]

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 T-cell lymphomas. Rebiopsy if consult material is nondiagnostic.**
- **A core biopsy of bone marrow or liver is required for diagnosis.[c] Bone marrow aspirate, FNA biopsy of liver, or evaluation of peripheral blood smear or peripheral blood evaluation may be helpful but are not alone sufficient for diagnosis.**
- **Adequate immunophenotyping to establish diagnosis[d,e]**
  - **IHC panel may include: CD20, CD3, CD10, Ki-67, CD5, CD30, CD2, CD4, CD8, CD7, CD56, TCRβ, TCRδ, TIA-1, or granzyme B**
  - **Cell surface marker analysis by flow cytometry may include: kappa/lambda, CD45, CD3, CD5, CD19, CD10, CD20, CD30, CD4, CD8, CD7, CD2, TCRαβ, or TCRɣδ**
- **EBER-ISH**

USEFUL IN CERTAIN CIRCUMSTANCES:

- **Molecular analysis to detect[d] clonal *TCR* gene rearrangements or other assessment of clonality.[f]**
- **Karyotype to establish clonality and investigate the presence of isochromosome 7q and trisomy 8.**
- **FISH for isochromosome 7q and trisomy 8.**
- **NGS panel may include *STAT3*, *STAT5B*, *PIK3CD*, *SETD2*, *INO80*, *TET3*, and *SMARCA2.***

→ **Workup (HSTCL-2)**

[a] It is preferred that treatment occur at centers with expertise in the management of this disease.
[b] Principles of Molecular Analysis in T-Cell Lymphomas (TCLYM-A).
[c] If the results are equivocal, core biopsy of spleen or splenectomy could be considered in centers with expertise.
[d] Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (TCLYM-E).
[e] Typical immunophenotype: CD3+, generally TCRδ+ and TCRβ- (GM3 positive, βF-1 negative), CD4 -, CD8-/+, CD56 +/-, CD5-.
[f] Clonal *TCR* gene rearrangements alone are not sufficient for diagnosis, as these can also be seen in patients with non-malignant conditions. Results should be interpreted in the context of overall presentation. See Principles of Molecular Analysis in T-Cell Lymphomas (TCLYM-A).

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

WORKUP

ESSENTIAL:
- **H&P examination; full skin examination; 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**
- **HLH workup (TCLYM-B 2 of 3)**
- **Uric acid**
- **FDG-PET/CT scan[g] and/or C/A/P CT with contrast of diagnostic quality**
- **Echocardiogram or MUGA scan if anthracycline-based regimen is indicated**
- **Pregnancy testing in those of childbearing potential (if chemotherapy or RT is planned)**
- **HLA typing**

USEFUL IN CERTAIN CIRCUMSTANCES
- **Neck CT with contrast**
- **Head CT or MRI with contrast**
- **HIV testing**
- **Hepatitis B and C testing**
- **Consider quantitative EBV PCR**
- **Discuss fertility preservation[h]**
- **Assessment of HTLV-1/2[i] by serology or other methods as clinically indicated**

→ First-Line Therapy (HSTCL-3)

[g] Patients with T-cell lymphomas often have extranodal disease, which may be inadequately imaged by CT. PET scan may be preferred in these instances.
[h] Fertility preservation options include: sperm banking, semen cryopreservation, IVF, or ovarian tissue or oocyte cryopreservation.
[i] See map for prevalence of HTLV-1/2 by geographic region. HTLV-1/2 has been described in patients in non-endemic areas.

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

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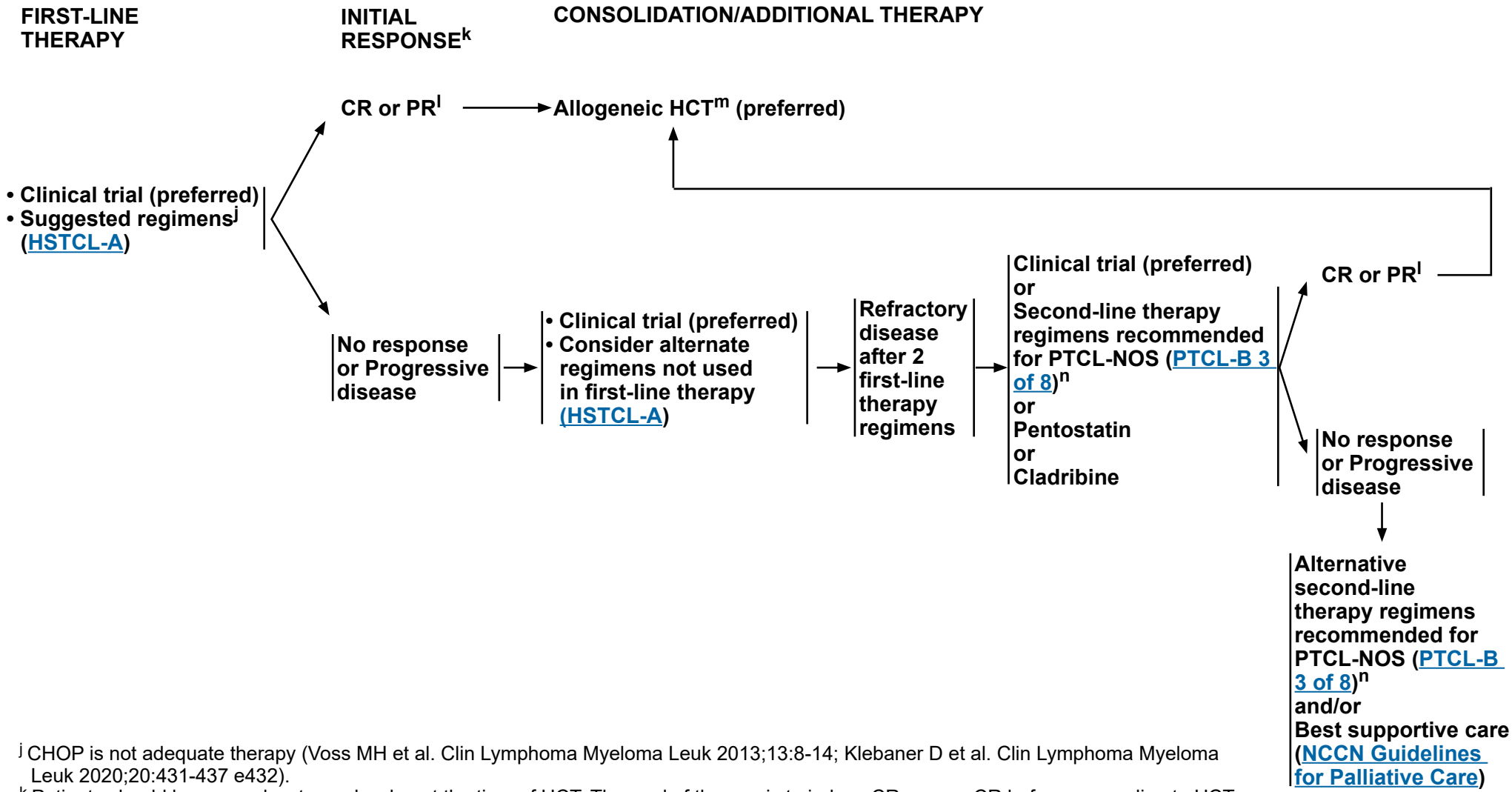


[j] CHOP is not adequate therapy (Voss MH et al. Clin Lymphoma Myeloma Leuk 2013;13:8-14; Klebaner D et al. Clin Lymphoma Myeloma Leuk 2020;20:431-437 e432).
[k] Patients should have very low tumor burden at the time of HCT. The goal of therapy is to induce CR or near CR before proceeding to HCT. Full-course chemotherapy may not be needed to achieve adequate response to allow HCT.
[l] PET scan alone is inadequate for response assessment. PET-negative response should be confirmed by bone marrow biopsy and in selected cases by liver biopsy. HSTCL is non-nodal and Lugano response criteria do not apply.
[m] Consider autologous HCT if unfit or lacking a suitable donor.
[n] Responses have been observed with alemtuzumab, pralatrexate, and ESHAP.

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

SUGGESTED TREATMENT REGIMENS

FIRST-LINE THERAPY/ADDITIONAL THERAPY[a,b]
• Clinical trial (preferred) Preferred regimen • ICE Other recommended regimens (alphabetical order) • DHA (dexamethasone and cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) • Dose-adjusted EPOCH • HyperCVAD alternating with high-dose methotrexate and cytarabine • IVAC (ifosfamide, etoposide, and cytarabine) Useful in certain circumstances (alphabetical by category) • Alemtuzumab[c] + pentostatin • CHOEP • Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone) for CD30+ cases[d] (category 2B)

[a] CHOP is not adequate therapy (Voss MH et al. Clin Lymphoma Myeloma Leuk 2013;13:8-14; Klebaner D et al. Clin Lymphoma Myeloma Leuk 2020;20:431-437 e432).
[b] See Supportive Care (TCLYM-B).
[c] While alemtuzumab is no longer commercially available, it may be obtained for clinical use. CMV monitoring or prophylaxis is recommended (Supportive Care TCLYM-B).
[d] Patients with HSTCL were eligible for the ECHELON-2 study [Horwitz S, O'Conner OA, Pro B, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. Lancet 2019;393:229-240], but no patients with HSTCL were enrolled.

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

DIAGNOSIS[a,b]

ESSENTIAL:

- **Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.**
- **Excisional or incisional biopsy is preferred over core needle biopsy. An FNA biopsy alone is not sufficient for the initial diagnosis of lymphoma.[c] 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[d,e]**
  - **IHC panel: For high clinical suspicion of NK/T-cell lymphoma, initial panel should include: CD2, cCD3ε, CD5, CD56, TIA1**
  - **Cell surface marker analysis by flow cytometry may include: CD2, CD3, CD4, CD5, CD7, CD8, CD56, TCRαβ, TCRγδ**
- **EBER-ISH[f]**

USEFUL IN CERTAIN CIRCUMSTANCES:

- **Molecular analysis to detect clonal *TCR* gene rearrangements or other assessment of clonality[g]**
- **IHC panel:**
  - **B-cell lineage: CD20**
  - **T-cell lineage: CD7, CD8, CD4, granzyme B, TCRβ, TCRδ**
  - **Other: CD30, Ki-67**

SUBTYPES

- **Subtypes included:**
  - **ENKL, nasal type** → **Workup (ENKL-2)**
  - **Extranasal ENKL** → **Workup (ENKL-2)**
- **ANKL (ENKL-C)**

[a] It is preferred that treatment occur at centers with expertise in the management of this disease.
[b] Principles of Molecular Analysis in T-Cell Lymphomas (TCLYM-A).
[c] 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. It is useful to perform multiple nasopharyngeal biopsies even in areas not clearly involved.
[d] Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (TCLYM-E).
[e] Typical NK-cell immunophenotype: CD20-, CD2+, cCD3ε+ (surface CD3-), CD4-, CD5-, CD7-/+, CD8-/+, CD43+, CD45RO+, CD56+, TCRαß-, TCRγδ-, 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, CD5, CD7, CD8 variable, CD56+/-, EBER+, TCRαß+ or TCRγδ+, cytotoxic granule proteins +. *TCR* genes are clonally rearranged.
[f] Negative result should prompt pathology review for alternative diagnosis.
[g] Clonal *TCR* gene rearrangements alone are not sufficient for diagnosis, as these can also be seen in patients with non-malignant conditions. Results should be interpreted in the context of overall presentation. See Principles of Molecular Analysis in T-Cell Lymphomas (TCLYM-A).

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

WORKUP[a]

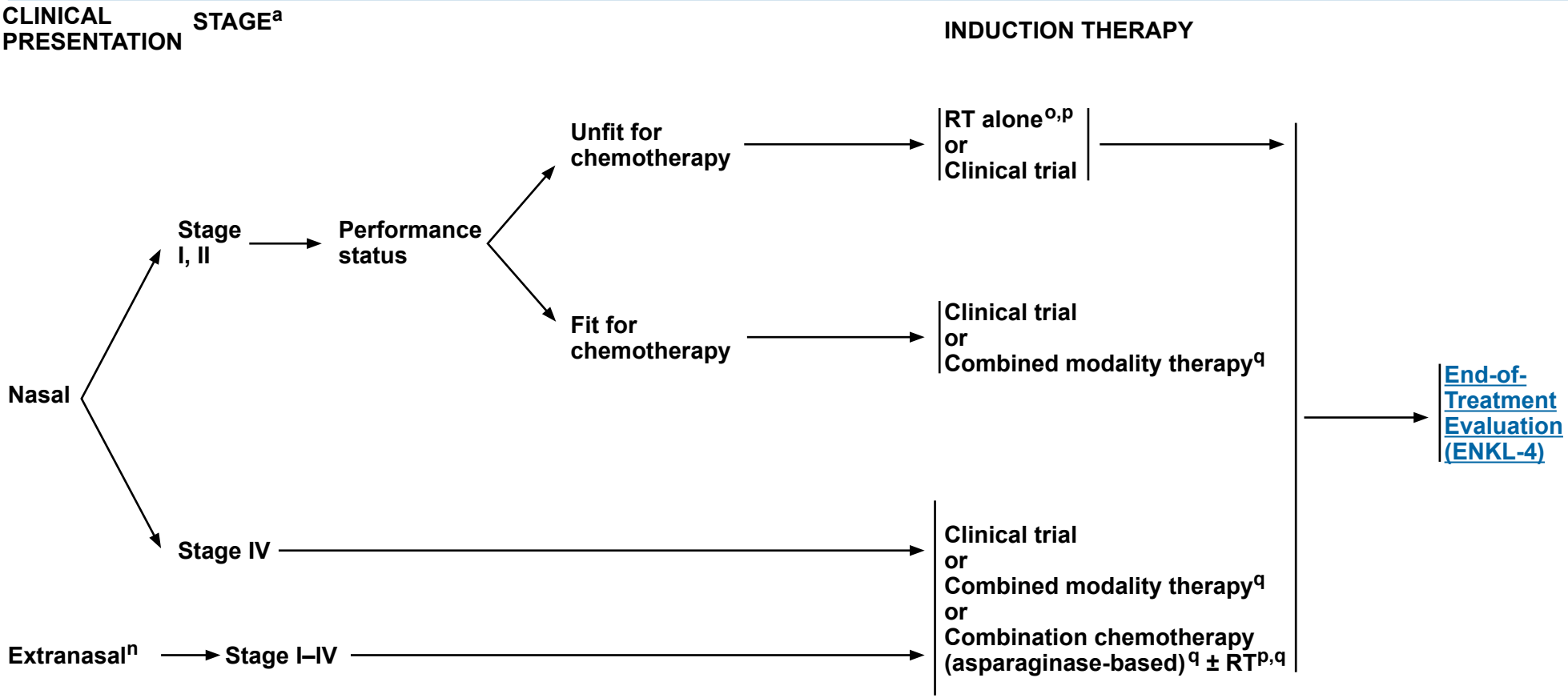
ESSENTIAL:
- **H&P examination with attention to node-bearing areas (including Waldeyer's ring), testicles, and skin**
- **Ear, nose, and throat (ENT) evaluation of nasopharynx**
- **Performance status**
- **B symptoms**
- **CBC with differential**
- **LDH**
- **Comprehensive metabolic panel**
- **Uric acid**
- **Bone marrow biopsy + aspirate[h]**
- **FDG-PET/CT scan[i] and/or C/A/P CT with contrast of diagnostic quality**
- **MRI ± CT pretreatment for RT planning of the nasal cavity, hard palate, anterior fossa, and nasopharynx**
- **Calculation of Prognostic Index of Natural Killer Lymphoma (PINK)[j]**
- **Echocardiogram or MUGA scan if anthracycline-based regimen is indicated**
- **EBV viral load[k] by quantitative EBV PCR**
- **Concurrent referral to RT for pretreatment evaluation**
- **Pregnancy testing in those of childbearing potential (if chemotherapy or RT is planned)**

USEFUL IN CERTAIN CIRCUMSTANCES:
- **HIV testing**
- **Hepatitis B and C testing**
- **Assessment of HTLV-1/2[m] by serology or other methods as clinically indicated**
- **Ophthalmologic exam**
- **Lumbar puncture with cerebrospinal fluid (CSF) analysis**
- **Discuss fertility preservation[l]**

→ **Induction Therapy (ENKL-3)**

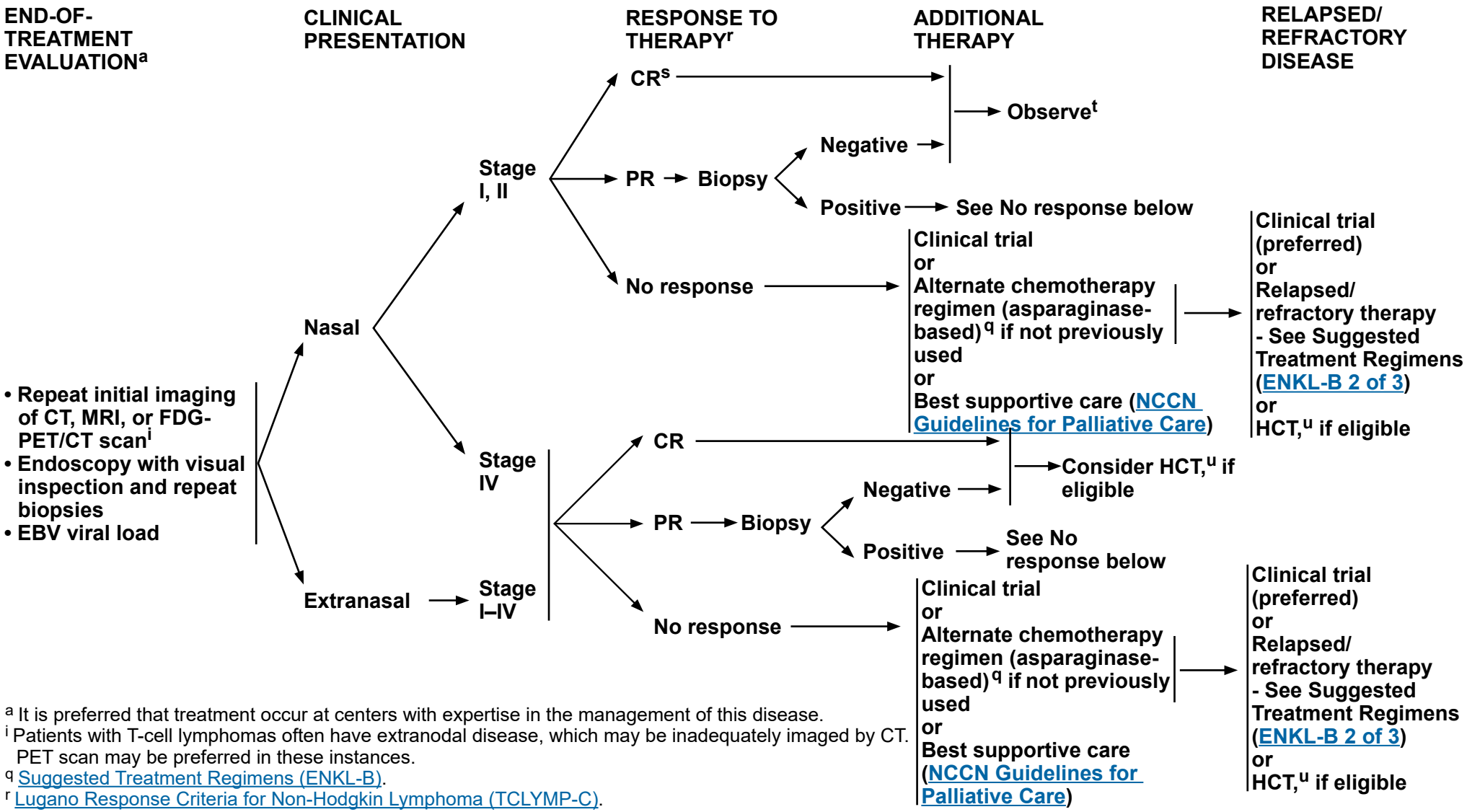
[a] It is preferred that treatment occur at centers with expertise in the management of this disease.
[h] Bone marrow aspirate - lymphoid aggregates are rare, and are considered involved if Epstein-Barr virus–encoded RNA (EBER)-1 positive; hemophagocytosis may be present.
[i] Patients with T-cell lymphomas often have extranodal disease, which may be inadequately imaged by CT. PET scan may be preferred in these instances.
[j] Prognostic Index of Natural Killer Lymphoma (PINK) (ENKL-A).
[k] EBV viral load is important in diagnosis and possibly in monitoring of disease. A positive result is consistent with NK/T-cell. Lack of normalization of EBV viremia should be considered indirect evidence of persistent disease.
[l] Fertility preservation options include: sperm banking, semen cryopreservation, IVF, or ovarian tissue or oocyte cryopreservation.
[m] See map for prevalence of HTLV-1/2 by geographic region. HTLV-1/2 has been described in patients in non-endemic areas.

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



[a] It is preferred that treatment occur at centers with expertise in the management of this disease.
[n] In rare circumstances of stage I_E primary cutaneous NKTL, involved-field RT for solitary lesions can be considered.
[o] RT as a part of initial therapy has an essential role in improved overall and disease-free survival in patients with localized ENKL, nasal type, in the upper aerodigestive tract.
[p] Principles of Radiation Therapy (TCLYM-D).
[q] Suggested Treatment Regimens (ENKL-B).

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



[a] It is preferred that treatment occur at centers with expertise in the management of this disease.
[i] Patients with T-cell lymphomas often have extranodal disease, which may be inadequately imaged by CT. PET scan may be preferred in these instances.
[q] Suggested Treatment Regimens (ENKL-B).
[r] Lugano Response Criteria for Non-Hodgkin Lymphoma (TCLYMP-C).
[s] Includes a negative ENT evaluation.
[t] May include H&P, ENT evaluation, FDG-PET/CT scan, and EBV viral load by quantitative PCR.
[u] There are no clear data to suggest whether allogeneic or autologous HCT is preferred and treatment should be individualized.

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

PROGNOSTIC INDEX OF NATURAL KILLER 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 2016;17:389-400.

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

SUGGESTED TREATMENT REGIMENS[a,b]

INDUCTION THERAPY	
Combination chemotherapy regimens (asparaginase-based)[c,d]	**Preferred regimens** • Modified SMILE (steroid [dexamethasone], methotrexate, ifosfamide, pegaspargase,[e] and etoposide) x 4–6 cycles for advanced stage • P-GEMOX (gemcitabine, pegaspargase, and oxaliplatin)[e] • DDGP (dexamethasone, cisplatin, gemcitabine, and pegaspargase)[d] x 3–6 cycles **Useful in certain circumstances** • AspaMetDex (pegaspargase, methotrexate, and dexamethasone)[e,f]
Combined modality therapy	**Preferred regimens** • Concurrent chemoradiation therapy (CCRT) ▸ RT[g] and DeVIC (dexamethasone, etoposide, ifosfamide, and carboplatin) x 3 cycles • Sequential chemoradiation ▸ Modified SMILE x 2–4 cycles followed by RT[f] ◊ Modified SMILE x 2 cycles is recommended for stage I–II disease • Sandwich chemoradiation[d] ▸ GELAD (gemcitabine, etoposide, pegaspargase, and dexamethasone)[e] x 2 cycles followed by RT followed by 2 cycles of GELAD ▸ P-GEMOX x 2 cycles followed by RT[g] followed by P-GEMOX x 2–4 cycles **Other recommended regimens** • CCRT followed by chemotherapy: RT[g] and cisplatin followed by VIPD (etoposide, ifosfamide, cisplatin, and dexamethasone) x 3 cycles • Sequential chemoradiation: DDGP x 3–6 cycles followed by RT[g] ▸ DDGP x 3 cycles is recommended for stage I–II disease

RT alone (if unfit for chemotherapy)[g]
• RT as a part of initial therapy has an essential role in improved overall and disease-free survival in patients with localized ENKL, nasal type, in the upper aerodigestive tract.

[a] See references for regimens on ENKL-B 3 of 3.
[b] See Supportive Care (TCLYM-B) for TLS prophylaxis and anti-infective prophylaxis.
[c] The panel recommends that the dose of pegaspargase should be capped at one vial (3750 IU). See Asparaginase Toxicity Management in the NCCN Guidelines for Acute Lymphoblastic Leukemia.
[d] Pegaspargase-based regimens are preferred. Treatment should be individualized based on patient's tolerance and comorbidities.
[e] Asparaginase Erwinia chrysanthemi (recombinant)-rywn can be substituted for pegaspargase in patients with systemic allergic reaction or anaphylaxis due to pegaspargase hypersensitivity.
[f] AspaMetDex is an option for selected patients who cannot tolerate more intensive chemotherapy.
[g] Principles of Radiation Therapy (TCLYM-D).

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

SUGGESTED TREATMENT REGIMENS[a,b]

RELAPSED/REFRACTORY THERAPY

Preferred regimens[h,i]
- Clinical trial
- Pembrolizumab
- Nivolumab

Other recommended regimens (alphabetical order)
- Single agents
  - Brentuximab vedotin for CD30+ disease
  - Pralatrexate
- Combination regimens (alphabetical order)
  - Asparaginase-based combination chemotherapy regimen (ENKL-B 1 of 3) not used in first-line therapy
  - DHA (dexamethasone and cytarabine) + platinum (cisplatin or oxaliplatin)
  - DHA (dexamethasone and cytarabine) + carboplatin (category 2B)
  - ESHA (etoposide, methylprednisolone, and cytarabine) + platinum (cisplatin or oxaliplatin)
  - GDP (gemcitabine, dexamethasone, and cisplatin)
  - GemOx (gemcitabine and oxaliplatin)
  - ICE (ifosfamide, carboplatin, and etoposide)

Useful in certain circumstances
- RT[g]
- Belinostat[j]
- Romidepsin[j]

[a] See references for regimens on ENKL-B 3 of 3.
[b] See Supportive Care (TCLYM-B) for TLS prophylaxis and anti-infective prophylaxis.
[g] Principles of Radiation Therapy (TCLYM-D).
[h] Clinical trial is the preferred relapsed/refractory option. In the absence of a clinical trial, pembrolizumab or nivolumab are appropriate options.
[i] The use of checkpoint inhibitors prior to allogeneic HCT may result in increased transplantation-related mortality and severe hyperacute GVHD.
[j] Reports of EBV reactivation have been seen with histone deacetylase (HDAC) inhibitors; consider monitoring.

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

SUGGESTED TREATMENT REGIMENS
REFERENCES

Combination Chemotherapy Regimens

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.

Ghione P, Qi S, Imber BS, et al. Modified SMILE (mSMILE) and intensity-modulated radiotherapy (IMRT) for extranodal NK-T lymphoma nasal type in a single-center population. Leuk Lymphoma 2020;61:3331-3341.

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.

Wang X, Zhang L, Liu X, et al. Efficacy and safety of a pegasparaginase-based chemotherapy regimen vs an L-asparaginase-based chemotherapy regimen for newly diagnosed advanced extranodal natural killer/T-cell lymphoma: A randomized clinical trial. JAMA Oncol 2022;8:1035-1041.

Zhu Y, Tian S, Xu L, M, et al. GELAD chemotherapy with sandwiched radiotherapy for patients with newly diagnosed stage IE/IIE natural killer/T-cell lymphoma: a prospective multicentre study. Br J Haematol 2022;196:939-946.

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 2017;35:32-39.

Sequential Chemoradiation

Ghione P, Qi S, Imber BS, et al. Modified SMILE (mSMILE) and intensity-modulated radiotherapy (IMRT) for extranodal NK-T lymphoma nasal type in a single-center population. Leuk Lymphoma 2020;61:3331-3341.

Zhang L, Wang Y, Li X, et al. Radiotherapy vs sequential pegaspargase, gemcitabine, cisplatin and dexamethasone and radiotherapy in newly diagnosed early natural killer/T cell lymphoma: A randomized, controlled, open label, multicenter study. Int J Cancer 2021;148:1470 1477.

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.

Wu T, Yang Y, Zhu SY, et al. Risk-adapted survival benefit of IMRT in early-stage NKTCL: A multicenter study from the China Lymphoma Collaborative Group. Blood Adv 2018;2:2369-2377.

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.

Chan TSY, Li J, Loong F, et al. PD1 blockade with low-dose nivolumab in NK/T cell lymphoma failing L-asparaginase: efficacy and safety. Ann Hematol 2018;97:193-196.

See PTCL-B (8 of 8) for references for combination regimens.

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

AGGRESSIVE NK-CELL LEUKEMIA (ANKL)

Overview and Definition:

- **ANKL is a rare leukemic form of an NK cell neoplasm with an aggressive clinical course.**
- **ANKL predominantly occurs in younger patients with a median age of 40 years, frequently presenting with B symptoms and concomitant HLH. Patients can also have hepatosplenomegaly and lymphadenopathy.**
- **In comparison to ENKL, ANKL does not usually have nasal or skin involvement.**
- **EBV-associated T- and NK-cell LPD, including chronic active EBV infection (CAEBV), can progress to ANKL.**
- **The diagnosis of ANKL is most frequently reached by bone marrow biopsy.**
- **Main differential diagnosis includes chronic LPD of NK cells (sometimes referred to as NK-LGL), CAEBV, EBV-positive T-cell and NK-cell lymphoproliferative diseases of childhood, ENKL, and rarely other EBV-associated T-cell lymphomas.**
- **Morphology of the malignant NK cell can be similar to that seen in LGLL. Typically, in ANKL the malignant cells are infected by EBV and therefore have detectable Epstein–Barr virus–encoded RNAs (EBERs) (ie, EBER-ISH positive). Similar to ENKL, quantifying EBV-DNA in peripheral blood can be useful at diagnosis and possibly in monitoring of disease. Expression of CD16 is characteristic of ANKL contrary to ENKL, suggesting a distinct differentiation stage of NK cells.[1,2]**
- **ANKL is thought to have genetic differences as compared to ENKL.[2] Mutations in the *JAK/STAT* pathway have been observed frequently, including *STAT3* (TCLYM-A 3 of 4). Contrary to ENKL, *JAK3* mutations have not been identified in ANKL.**

General Principles of Management and Treatment:

- **Treatment with anthracycline-based regimens is typically ineffective. Consider combination chemotherapy regimens (asparaginase-based) on ENKL-B (1 of 3).[3]**
- **The NCCN Panel favors consolidation with allogeneic HCT over autologous HCT for patients in first remission.[4,5]**

[1] Suzuki R, Suzumiya J, Nakamura S, et al. Aggressive natural killer-cell leukemia revisited: large granular lymphocyte leukemia of cytotoxic NK cells. Leukemia 2004;18:763-770.

[2] Nakashima Y, Tagawa H, Suzuki R, et al. Genome-wide array-based comparative genomic hybridization of natural killer cell lymphoma/leukemia: different genomic alteration patterns of aggressive NK-cell leukemia and extranodal NK/T-cell lymphoma, nasal type. Genes Chromosomes Cancer 2005;44:247-255.

[3] Jung KS, Cho SH, Kim SJ, et al. L-asparaginase-based regimens followed by allogeneic hematopoietic stem cell transplantation improve outcomes in aggressive natural killer cell leukemia. J Hematol Oncol 2016;9:41.

[4] Ishida F, Ko YH, Kim WS, et al. Aggressive natural killer cell leukemia: therapeutic potential of L-asparaginase and allogeneic hematopoietic stem cell transplantation. Cancer Sci 2012;103:1079-1083.

[5] Hamadani M, Kanate AS, DiGilio A, et al. Allogeneic Hematopoietic Cell Transplantation for Aggressive NK Cell Leukemia. A Center for International Blood and Marrow Transplant Research Analysis. Biol Blood Marrow Transplant 2017;23:853-866.

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

PRINCIPLES OF MOLECULAR ANALYSIS IN T-CELL LYMPHOMAS[a]

- **Genetic testing, including high-throughput sequencing (HTS), array-based comparative genomic hybridization (CGH), NGS, karyotype, or FISH to detect somatic mutations or genetic abnormalities are often informative and in some cases essential for an accurate and precise diagnostic and prognostic assessment of T-cell lymphomas.**

TCR Gene Rearrangements

- ***TCR* gene rearrangement testing is recommended to support a diagnosis of T-cell lymphomas.**
- **Diseases:**
  - **PTCLs; T-LGLL; T-PLL; ENKL; and HSTCL.**
- **Description:**
  - ***TCR* gene rearrangement is indicative of T-cell clonal expansion. The test targets the gamma and/or beta *TCR* genes using PCR methods with capillary or gel electrophoresis detection methods. Alternatively, HTS methods are increasingly used. HTS methods are more sensitive, precise, and capable of providing a unique sequence of the T-cell clone, which allows for comparison and confirmation of disease evolution and monitoring during remission. Clonal T-cell expansions can also be detected using V beta families in blood or tissue with flow cytometry methods.**
- **Diagnostic value:**
  - **Clonal *TCR* gene rearrangements without histopathologic and immunophenotypic evidence of abnormal T-cell population does not constitute a diagnosis of T-cell lymphoma since it can be identified in patients with non-malignant conditions. Conversely, a negative result does not exclude the diagnosis of T-cell lymphoma, which occasionally may fail *TCR* amplification. Nonetheless, it often provides essential information and increased precision for many of these complex diagnoses.**
- **Prognostic value:**
  - **Identification of clonal *TCR* gene rearrangement has no definitive established prognostic value; however, it could be helpful when used to determine clinical staging or assess relapsed or residual disease.**

ALK Gene Rearrangement

- **A subset of CD30-positive ALCLs expresses ALK by IHC. ALK expression is often associated with t(2;5)(p23;q35), leading to the fusion of *NPM1* to ALK and resulting in a chimeric protein.**
- **Detection:**
  - **FISH using probes to *ALK* (2p23)**
  - **Targeted messenger RNA (mRNA) sequencing**
- **Diagnostic value:**
  - **The current WHO5 classification of ALCLs includes two entities distinguishing ALK-positive and ALK-negative variants.**
- **Prognostic value:**
  - **Systemic ALK-positive ALCL with t(2;5) and ALK-negative ALCL with *DUSP22* rearrangement (to a lesser extent) have been associated with a favorable prognosis.**
  - **ALK inhibition can be an effective therapeutic strategy in ALK-positive ALCL.**

Continued

[a] See References on TCLYM-A 4 of 4.

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

PRINCIPLES OF MOLECULAR ANALYSIS IN T-CELL LYMPHOMAS[a]

DUSP22-IRF4 Gene Rearrangement

- Testing for *DUSP22* rearrangement is considered if CD30-positive ALCL, ALK negative is diagnosed.
- Diseases:
  - PTCLs
- Description:
  - *DUSP22* is a tyrosine/threonine/serine phosphatase that may function as a tumor suppressor gene. *DUSP22* inactivation contributes to the development of PTCLs.
- Detection:
  - FISH using probes to *DUPS22-IRF4* gene region at 6p25.3.
- Diagnostic value:
- *DUSP22* rearrangements are associated with a newly recognized variant of ALK-negative ALCL.
- Prognostic value:
  - ALCL, ALK-negative with a *DUSP22* rearrangement has been variably associated with a prognosis more similar to ALK-positive disease and treatment according to the ALCL, ALK-positive algorithm may be considered for ALK-negative ALCL with *DUSP22* rearrangement.

TP63 Rearrangement

- *TP63* gene rearrangements encoding p63 fusion proteins define a subset of ALK-negative ALCL cases and are associated with aggressive course.
- Detection:
  - FISH using probes to *TP63* (3q28) and *TBL1XR1*::*TP63*
  - Targeted mRNA sequencing
- Disease:
  - ALK-negative ALCL
- Diagnostic value:
  - To identify ALK-negative ALCL associated with aggressive course

TCL1 and *TRA* Translocation

- Most T-PLL have an inversion or translocation of chromosome 14 with breakpoints in the long arm at q11 and q32 [inv(14)(q11q32) and t(14;14)(q11;q32)]. These translocations and inversions cause gene overexpression due to juxtaposition with *TCRα* or *TCRß* regulatory elements and activate the oncogenes *TCL1A* and *MTCP1-B1*.
- Disease:
  - T-PLL
- Diagnostic value:
  - Distinguishing T-PLL from Sézary syndrome or ATLL
- Detection:
  - FISH, chromosomal karyotype

Continued

[a] See References on TCLYM-A 4 of 4.

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

PRINCIPLES OF MOLECULAR ANALYSIS IN T-CELL LYMPHOMAS[a]

***TET2/IDH1/IDH2/RHOA/DNMT3A* Mutations**

- High incidence of somatic mutations in *IDH2* and *TET2* genes has been identified in AITLs. *IDH2* and *TET2* encode for proteins involved in epigenetic regulation, suggesting that disruption of gene expression regulation by methylation and acetylation may be involved in AITL development and/or progression. Additional genetic findings include the presence of mutations affecting *RHOA G17V* and *DNMT3A*.
- Disease:
  - Suspected AITL versus other PTCL.
- Detection method:
  - Bidirectional sequencing of the entire coding or selected exons in the genes *IDH1, IDH2, DNMT3A, TET2,* and *RHOA*.
- Diagnostic value:
  - Diagnosis of AITL versus other PTCLs. This pathway has been preliminarily associated with higher rates of response to histone deacetylase (HDAC) inhibitors and other epigenetic modifiers. Clinical trials of this approach are currently ongoing.

***STAT3/STAT5B* Mutations**

- *STAT3* mutation testing is recommended under certain circumstances for diagnosis of LGLL and NK leukemias. *STAT5B* mutations may be associated with aggressive subtypes.
- Diseases:
  - LGLL and ANKL. Similar mutations are also reported in HSTCL.
- Description:
  - *STAT3* mutations have been identified in approximately 50% of LGLL and NK leukemias, including *Y640F*, *N647I*, *E638Q*, *I659L*, and *K657R* (1/18, 5.6%).
- Detection:
  - Bidirectional sequencing of *STAT3* (exons 13–21) and/or *STAT5B.*
- Diagnostic value:
  - Diagnosis of LGLL and ANKL.

[a] See References on TCLYM-A 4 of 4.

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

PRINCIPLES OF MOLECULAR ANALYSIS IN T-CELL LYMPHOMAS
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Chiarle R, Voena C, Ambrogio C, Piva R, et al. The anaplastic lymphoma kinase in the pathogenesis of cancer. Nat Rev Cancer 2008;8:11-23.

De Schouwer PJ, Dyer MJ, Brito-Babapulle VB, et al. T-cell prolymphocytic leukemia: antigen receptor gene rearrangement and a novel mode of MTCP1-B1 activation. Br J Haematol 2000;110:831-838.

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

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.**

- **TLS features:**
  - **Consider TLS prophylaxis for patients with the following risk factors:**
    - ◊ **Spontaneous TLS**
    - ◊ **High tumor burden or bulky disease**
    - ◊ **Elevated white blood cell (WBC) count**
    - ◊ **Bone marrow involvement**
    - ◊ **Pre-existing elevated uric acid**
    - ◊ **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 (essential)**
  - **First-line and at retreatment for hyperuricemia**
    - ◊ **Glucose-6-phosphate dehydrogenase (G6PD) testing is required prior to use of rasburicase. Rasburicase is contraindicated in patients with a history consistent with G6PD. In these patients, rasburicase should be substituted with allopurinol.**
    - ◊ **Low-Risk Disease:**
      Allopurinol or febuxostat beginning 2–3 days prior to chemoimmunotherapy and continued for 10–14 days
    - ◊ **Intermediate-Risk Disease: Stage I/II and LDH <2X upper limit of normal (ULN):**
      Allopurinol or febuxostat
      OR
      Rasburicase if renal dysfunction and uric acid, potassium, and/or phosphate >ULN
    - ◊ **High-Risk Disease: Stage III/IV and/or LDH ≥2X ULN:**
      Rasburicase
  - **Rasburicase (Doses of 3–6 mg are usually effective.[a] One dose of rasburicase is frequently adequate. Re-dosing should be individualized.) is indicated for patients with any of the following risk factors:**
    - **Urgent need to initiate therapy in a high-bulk patient**
    - **Situations where adequate hydration may be difficult or impossible**
    - **Acute renal failure**
  - **If TLS is untreated, its progression may cause acute kidney failure, cardiac arrhythmias, seizures, loss of muscle control, and death.**

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

Continued

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

SUPPORTIVE CARE

Hemophagocytic Lymphohistiocytosis (HLH)[b]

- Syndrome of extreme immune activation resulting in life-threatening inflammation

- Clinical signs and symptoms may include: (these may overlap with features of underlying lymphoma)
  - Fever
  - Hepatosplenomegaly
  - Cytopenias (affecting 2 of 3 lineages in the peripheral blood)
    - Hemoglobin <9 g/dL
    - Platelets <100 x 10^3/mL
    - Neutrophils <1 x 10^3/mL
  - Hypertriglyceridemia and/or hypofibrinogenemia
    - Fasting triglycerides >3.0 mmol/L (ie, >265 mg/dL)
    - Fibrinogen <1.5 g/L
  - Hemophagocytosis in bone marrow or spleen or lymph nodes
  - Ferritin >500 ng/mL
  - sIL-2R (also known as soluble CD25 [sCD25]) >2400 U/mL
  - Elevated transaminases and bilirubin
  - Elevated LDH
  - Elevated D-dimer
  - Elevated CSF cells and/or protein

- Diagnostic evaluation[c]
  - Labs including CBC with differential, triglycerides, fibrinogen, ferritin, sCD25, liver function tests (LFTs), LDH, and D-dimer
  - Bone marrow biopsy
    - Consider repeat bone marrow biopsy if strong suspicion of HLH
  - Consider liver biopsy

- Management[d]
  - Recommend expert consultation
  - Treatment of the underlying T-cell lymphoma with preference for etoposide- and steroid-containing regimens. Start with HLH-directed therapy if cytopenias preclude standard anti-lymphoma therapy, and then initiate standard anti-lymphoma therapy when cytopenias improve.
  - Antiviral therapy - See Monoclonal Antibody Therapy and Viral Reactivation (TCLYM-B 3 of 4)

[b] HLH in adults is often associated with an underlying T-cell lymphoma. Diagnostic workup to confirm the lymphoma subtype and prompt initiation of treatment for underlying T-cell lymphoma is often required.

[c] Consider optimized HLH inflammatory (OHI) index [combined elevation of sCD25 (>3900 U/mL) and ferritin (>1000 ng/mL)] to simplify the diagnosis of HLH in patients with hematologic malignancies (Zoref-Lorenz A, Murakami J, Hofstetter L, et al. An improved index for diagnosis and mortality prediction in malignancy-associated hemophagocytic lymphohistiocytosis. Blood 2022;139:1098-1110).

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Continued

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

SUPPORTIVE CARE

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

Monoclonal Antibody Therapy and Viral Reactivation

- **Alemtuzumab (anti-CD52 antibody):**
  - **CMV reactivation:**
    - **The current appropriate management is controversial; some NCCN Member Institutions use ganciclovir (PO or IV) preemptively if viremia is present, others only if viral load is rising.**
    - **CMV viremia should be measured by quantitative PCR at least every 2–3 weeks.**
  - **Anti-infective prophylaxis**
    - **Herpes simplex virus (HSV) prophylaxis with acyclovir or equivalent.**
    - **Pneumocystis jiroveci pneumonia (PJP) prophylaxis with sulfamethoxazole/trimethoprim or equivalent.**
    - **Consider screening and treatment (if needed) for strongyloidiasis in patients with ATLL.**
    - **Consider antifungal prophylaxis.**
    - **Consultation with an infectious disease expert may be necessary. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.**
  - **Consider evaluating for CD52 expression before initiating treatment with alemtuzumab-based regimens.**
- **Brentuximab vedotin (anti-CD30 antibody-drug conjugate)**
  - **Progressive multifocal leukoencephalopathy (PML):**
    - **Caused by reactivation of the John Cunningham virus (JCV) and is usually fatal.**
    - **Diagnosis made by PCR of CSF and in some cases brain biopsy.**
    - **Clinical indications may include changes in behavior such as confusion, dizziness or loss of balance, difficulty talking or walking, and vision problems.**
    - **No known effective treatment.**

Continued

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

SUPPORTIVE CARE

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

Tumor Flare Reactions

- **Management of tumor flare is recommended for patients receiving lenalidomide.**
- **Tumor flare reactions are painful lymph node enlargements or lymph node enlargements with evidence of local inflammation, occurring with treatment initiation; may also be associated with spleen enlargement, low-grade fever, and/or rash.**
- **Treatment: Steroids (eg, prednisone 25–50 mg PO for 5–10 days); antihistamines for rash and pruritus (eg, cetirizine 10 mg PO once daily or loratadine 10 mg PO daily).**
- **Prophylaxis: Consider in patients with bulky lymph nodes (>5 cm); administer steroids (eg, prednisone 20 mg PO for 5–7 days followed by rapid taper over 5–7 days).**

Prevention of Pralatrexate-Induced Mucositis[e,f,g]

- **Vitamin B12 (cyanocobalamin) at a dose of 1000 mcg intramuscular to be started no more than 10 weeks prior to starting therapy with pralatrexate and then every 8–10 weeks.**
- **Oral folic acid 1–1.25 mg daily to be started within 10 days of starting therapy and continuing for 30 days after the last dose of pralatrexate.**
- **Consider use of oral leucovorin 25 mg 3 times daily for 2 consecutive days (total of 6 doses), starting 24 hours after each dose of pralatrexate.**

Adverse Events Associated with Mogamulizumab:

- **Graft-versus-host disease (GVHD): A retrospective study showed a particularly high risk of developing GVHD in patients proceeding to allogeneic HCT within 50 days of mogamulizumab.[h]**
- **Mogamulizumab-associated rash (MAR): Mogamulizumab has been associated with a drug eruption (termed as MAR) that can clinically mimic cutaneous T-cell lymphoma. Skin biopsy is recommended to distinguish progression of disease versus drug eruption.[i]**

[e] Mould DR, Sweeney K, Duffull SB, et al. A population pharmacokinetic and pharmacodynamic evaluation of pralatrexate in patients with relapsed or refractory non-Hodgkin's or Hodgkin's lymphoma. Clin Pharmacol Ther 2009;86:190-196.
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Note: All recommendations are category 2A unless otherwise indicated.

LUGANO RESPONSE CRITERIA FOR NON-HODGKIN 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 TCLYM-C 3 of 3
Continued

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

LUGANO RESPONSE CRITERIA FOR NON-HODGKIN 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 TCLYM-C 3 of 3
Continued

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

LUGANO RESPONSE CRITERIA FOR NON-HODGKIN 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, eg, liver, spleen, kidneys, lungs, etc, gastrointestinal involvement, cutaneous lesions of those noted on palpation.
Non-measured lesions – Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant, measurable or which do not meet the requirements for measurability, but are still considered abnormal. As well as truly assessable disease which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses and other lesions that cannot be confirmed and followed by imaging.

 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;32:3059-3068.

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

PRINCIPLES OF RADIATION THERAPY[a]

General Principles

- **Treatment with photons, electrons, or protons may all be appropriate, depending on clinical circumstances.**
- **Modern general principles of RT using ISRT should be followed.**
- **Advanced RT technologies such as intensity-modulated RT (IMRT), breath hold or respiratory gating, image-guided RT (IGRT), or proton therapy may offer significant and clinically relevant advantages in specific instances to spare important organs at risk (OARs) 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 OARs 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 IGRT 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 greater than 10 years to evolve. In light of that, the modalities and techniques that are found to best reduce the doses to the OARs in a clinically meaningful way without compromising target coverage should be considered.**
- **Radiation dose constraints: Recommendations for normal tissue dose constraints can be found in the Principles of Radiation Therapy in the NCCN Guidelines for Hodgkin Lymphoma.**

[a] See references on TCLYM-D 4 of 4.

Continued

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

PRINCIPLES OF RADIATION THERAPY[a]

Target Volumes:

- **ISRT for nodal disease**
  - ISRT is recommended as the appropriate field for non-Hodgkin lymphoma. Planning for ISRT requires modern CT-based simulation and planning capabilities. Incorporating other modern imaging such as 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 (eg, lungs, bone, muscle, 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.
  - 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 target volume (PTV) is an additional expansion of the CTV that accounts only for setup variations (see International Commission on Radiation Units and Measurements [ICRU] definitions).
  - The OARs 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 OARs.

- **ISRT for extranodal disease (excluding ENKL)**
  - Similar principles as for ISRT nodal sites (see above).
  - For most organs, the whole organ comprises the CTV (eg, stomach, salivary gland, thyroid). For other organs, including orbit, breast, lung, bone, and localized skin, partial organ RT may be appropriate.
  - Prophylactic irradiation is not required for uninvolved lymph nodes.

[a] See references on TCLYM-D 4 of 4.

Continued

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

PRINCIPLES OF RADIATION THERAPY[a]

- **ISRT for ENKL**
  - For optimal treatment planning, both contrast-enhanced CT and contrast-enhanced MRI are essential. An FDG-PET/CT scan is necessary for defining the presence of nodal disease.
  - The GTV is defined based on combined abnormalities identified on endoscopy, CT, and MRI.
  - The ISRT CTV should include the entire involved cavity and adjacent structures due to the high risk for submucosal spread.
    - ◊ For unilateral anterior or mid-nasal cavity, the CTV should include the bilateral nasal cavities, ipsilateral maxillary sinus, and bilateral anterior ethmoids.
    - ◊ For bilateral nasal cavity involvement, the CTV should include both maxillary sinuses.
    - ◊ If there is posterior nasal cavity involvement, the nasopharynx should be included in the CTV.
    - ◊ If there is anterior ethmoid involvement, the posterior ethmoids should be included in the CTV.
    - ◊ All involved paranasal sinuses should be included in the CTV.
    - ◊ Any areas of soft tissue extension should be included in the CTV.
    - ◊ Prophylactic irradiation is not required for uninvolved lymph nodes.
    - ◊ Experience combining newer chemotherapy regimens with smaller ISRT fields (ie, GTV with minimal expansion to define the CTV) is limited and the likelihood of local failure with these smaller fields is not known.
  - The PTV is an additional expansion of the CTV that accounts only for setup variations (see ICRU definitions).
  - The OARs 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 OARs.

[a] See references on TCLYM-D 4 of 4.

Continued

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

PRINCIPLES OF RADIATION THERAPY

General Dose Guidelines: (RT in conventional fraction sizes)

- **PTCL**
  - **Consolidation after chemotherapy CR: 30–36 Gy; PR: 40–50 Gy**
  - **RT as primary treatment for refractory or non-candidates for chemotherapy: 40–55 Gy**
  - **In combination with HCT: 20–36 Gy, depending on sites of disease and prior RT exposure**
- **BIA-ALCL: 24–36 Gy for local residual disease**
- **ENKL**
  - **RT alone as primary treatment (if unfit for chemotherapy): 50–55 Gy**
  - **RT in combination with chemotherapy: 45–56 Gy**
  - **Combined modality therapy (non–asparaginase-based):**
    - ◊ **CCRT:**
      - **50 Gy in combination with DeVIC (dexamethasone, etoposide, ifosfamide, and carboplatin)**
      - **50–54 Gy in combination with cisplatin followed by VIPD (etoposide, ifosfamide, cisplatin, and dexamethasone)**
    - ◊ **Sequential chemoradiation: Modified SMILE regimen followed by RT 45–50.4 Gy for stage I–II disease**
    - ◊ **Sandwich chemoradiation:**
      - **P-GEMOX (2 cycles) followed by RT 56 Gy followed by P-GEMOX (2–4 cycles)**
      - **GELAD (2 cycles) followed by RT 50-56 Gy followed by GELAD (2 cycles)**
- **Palliative RT: 20–36 Gy in 5–18 fractions**

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

USE OF IMMUNOPHENOTYPING/GENETIC TESTING IN DIFFERENTIAL DIAGNOSIS OF NK/T-CELL NEOPLASMS[a] (TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)

General Principles

- Morphology ± clinical features drive both the choice and the interpretation of special studies.
- Differential diagnosis is based on morphology ± clinical setting.
- Begin with a broad panel appropriate to morphologic diagnosis, limiting panel of antibodies based on the differential diagnosis.
  - Avoid "shotgun" panels of unnecessary antibodies unless a clinically urgent situation warrants.
- Add antigens in additional panels, based on initial results.
- Follow with genetic studies as needed.
- Return to clinical picture if immunophenotype + morphology are not specific.

T- or NK/T-cell antigens positive[b,c]
(CD2, CD3, CD5, CD7) (and B-cell antigens negative)

- Morphology
  - Anaplastic vs. non-anaplastic
  - Epidermotropic
- Clinical
  - Age (child, adult)
  - Location
    - ◊ Cutaneous
    - ◊ Extranodal noncutaneous (specific site)
    - ◊ Nodal
- Immunophenotype
  - CD30, ALK*, CD56, ßF1, cytotoxic granule proteins
  - CD4, CD8, CD5, CD7, TCRαß, TCRγδ, CD1a, TdT
  - Follicular T cells: CD10, BCL6, CD57, PD1/CD279, CXCL13, ICOS
  - Viruses: EBV, HTLV1 (clonal)
- Genetic testing
  - *ALK*, *TCR*, *HTLV1*

See Initial Morphologic, Clinical, and Immunophenotypic Analysis (TCLYM-E 2 of 5)

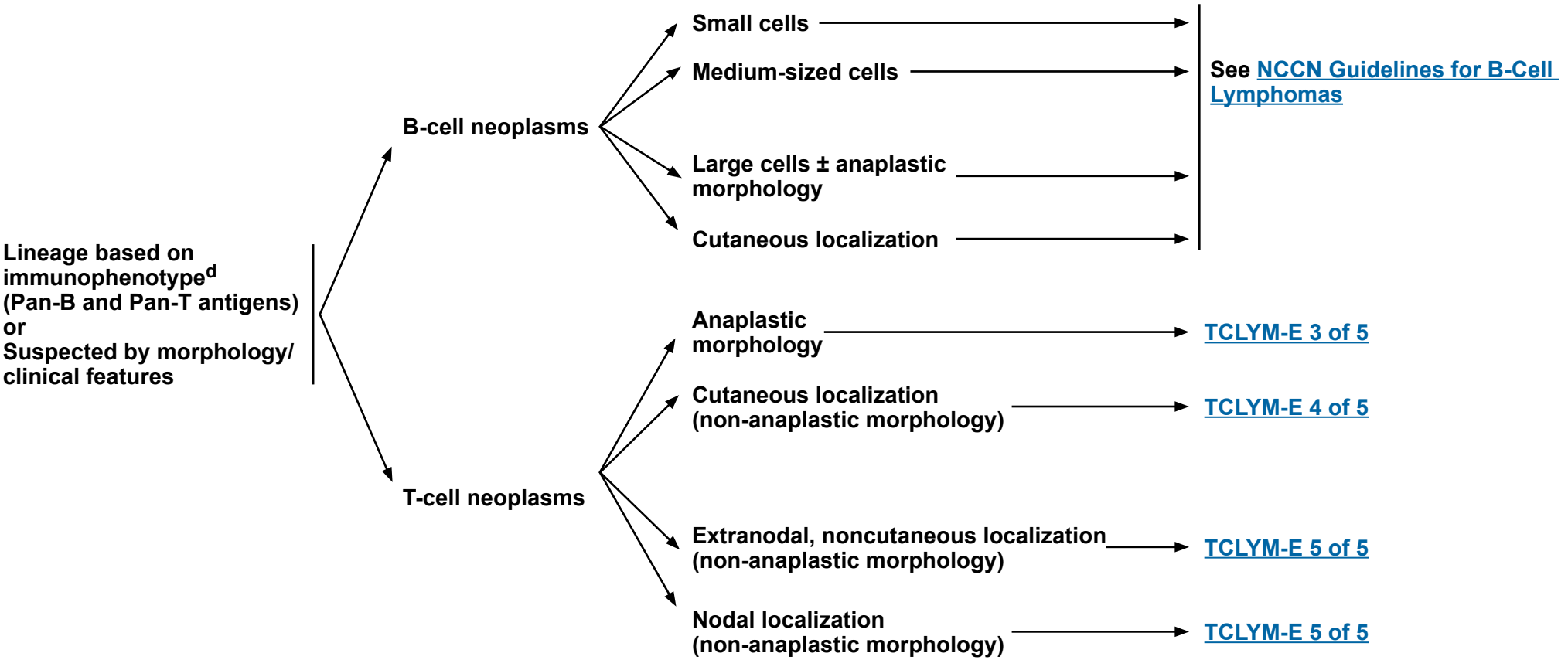
*Always do ALK if CD30+

[a] These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.
[b] Some lymphoid neoplasms may lack pan leukocyte (CD45), pan-B, and pan-T antigens. Selection of additional antibodies should be based on the differential diagnosis generated by morphologic and clinical features (eg, plasma cell myeloma, ALK+ DLBCL, plasmablastic lymphoma, anaplastic large cell lymphoma [ALCL], NK-cell lymphomas).
[c] Usually 1 pan-B (CD20) and 1 pan-T (CD3) markers are done unless a terminally differentiated B-cell or a specific PTCL is suspected.

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

USE OF IMMUNOPHENOTYPING/GENETIC TESTING IN DIFFERENTIAL DIAGNOSIS OF NK/T-CELL NEOPLASMS[a] (TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)

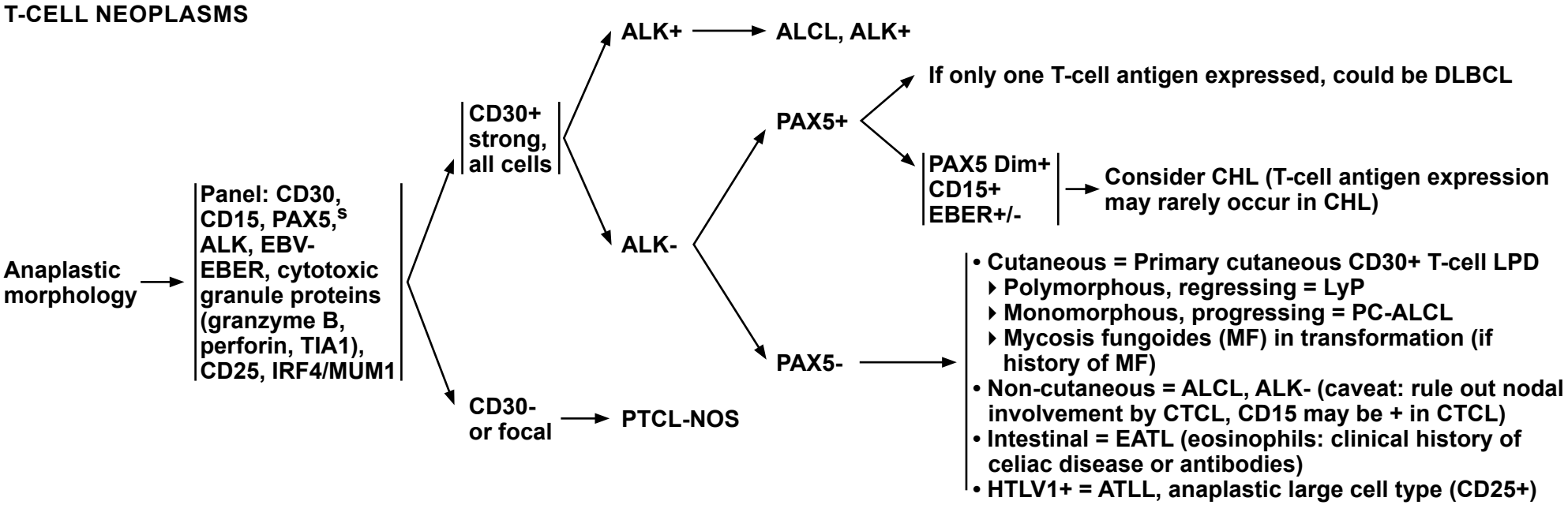
INITIAL MORPHOLOGIC, CLINICAL, AND IMMUNOPHENOTYPIC ANALYSIS



[a] These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.
[d] Initial panel will often include additional markers based on morphologic differential diagnosis and clinical features.

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

USE OF IMMUNOPHENOTYPING/GENETIC TESTING IN DIFFERENTIAL DIAGNOSIS OF NK/T-CELL NEOPLASMS[a] (TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)



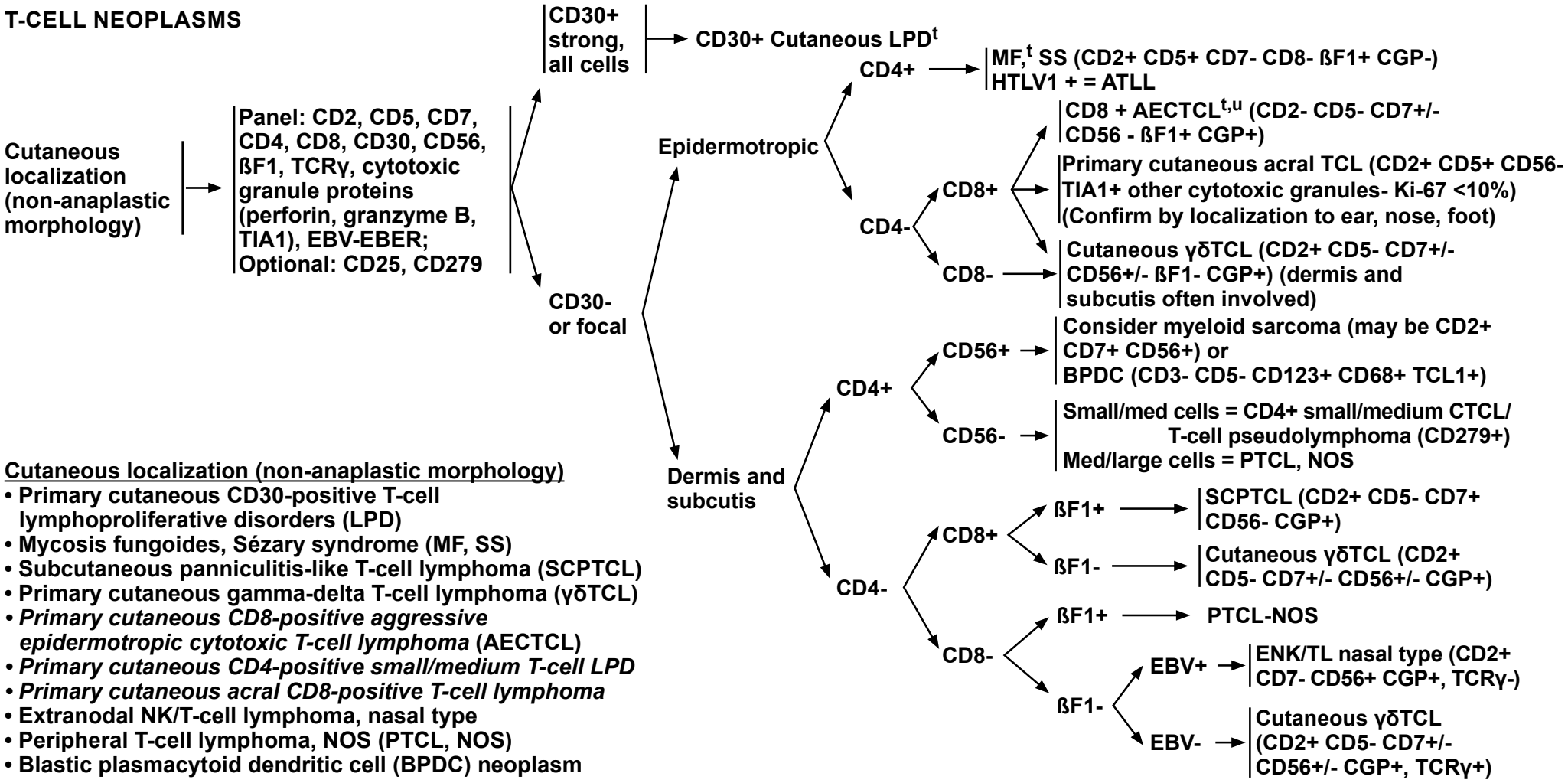
Anaplastic morphology
- Anaplastic large cell lymphoma (ALCL), ALK positive
- ALCL, ALK negative
- Adult T-cell leukemia/lymphoma (ATLL), anaplastic large cell type
- Enteropathy-associated T-cell lymphoma (EATL)
- Primary cutaneous CD30-positive T-cell LPD
  - Lymphomatoid papulosis (LyP)
  - Primary cutaneous ALCL (PC-ALCL)

[a] These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.

[s] Rare T-cell lymphomas may be CD20+ or PAX5+. Assessment of other Pan-T and -B markers is essential. The expression of multiple markers of 1 lineage and only 1 of the other lineages supports lineage assignment. PCR analysis may be required to determine lineage in such cases.

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

USE OF IMMUNOPHENOTYPING/GENETIC TESTING IN DIFFERENTIAL DIAGNOSIS OF NK/T-CELL NEOPLASMS[a]
(TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)



Cutaneous localization (non-anaplastic morphology)

- **Primary cutaneous CD30-positive T-cell lymphoproliferative disorders (LPD)**
- **Mycosis fungoides, Sézary syndrome (MF, SS)**
- **Subcutaneous panniculitis-like T-cell lymphoma (SCPTCL)**
- **Primary cutaneous gamma-delta T-cell lymphoma (γδTCL)**
- ***Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma* (AECTCL)**
- ***Primary cutaneous CD4-positive small/medium T-cell LPD***
- ***Primary cutaneous acral CD8-positive T-cell lymphoma***
- **Extranodal NK/T-cell lymphoma, nasal type**
- **Peripheral T-cell lymphoma, NOS (PTCL, NOS)**
- **Blastic plasmacytoid dendritic cell (BPDC) neoplasm**

[a] These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.
[t] A minority of MF cases can be CD30+, CD4-, CD8+/-, and TIA1+. ATLL may also be CD30+.
[u] AECTCL has distinctive morphology and clinical presentation.

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

USE OF IMMUNOPHENOTYPING/GENETIC TESTING IN DIFFERENTIAL DIAGNOSIS OF NK/T-CELL NEOPLASMS[a] (TO BE USED IN CONJUNCTION WITH CLINICAL AND MORPHOLOGIC CORRELATION)

Extranodal, noncutaneous localization (non-anaplastic morphology) → **Panel: CD2, CD3, CD4, CD5, CD7, CD8, CD30, CD56, ALK, ßF1, TCRγ, IRF4/MUM1, cytotoxic granule proteins (perforin, granzyme B, TIA1), EBV-EBER**

- **EBER+** → **ENKTCL (CD5- CD4- CD8- CD30- CD56+ CGP+, midline face, upper aerodigestive tract, testis, GI tract) (may have T-cell phenotype)**
- **EBER-**
  - **CD30+**
    - **ALK+** → **ALCL, ALK+ small cell or histiocyte-rich variants**
    - **ALK-** →
      - **Intestinal, other abdominal/visceral sites, celiac disease or markers positive = EATL (CD5- CD7- CD4- CD8+/- CD56+/- TIA1+ GRB+ Perf+)**
      - **Other sites, celiac disease markers negative = PTCL, NOS (usually less strongly CD30+)**
  - **CD30-** →
    - **Intestine, epidermorphic = MEITL**
    - **Liver, spleen, bone marrow sinuses, immune suppression = HSTCL (CD5- CD7- CD4- CD8- CD56+ TIA1+ GRB- Perf-)**
    - **Other sites = PTCL, NOS**

Extranodal, noncutaneous localization
- **Extranodal NK/T-cell lymphoma, nasal type (ENKTCL)**
- **Enteropathy-associated T-cell lymphoma (EATL)**
- **Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)**
- **Hepatosplenic T-cell lymphoma (HSTCL)**
- **Peripheral T-cell lymphoma, NOS (PTCL, NOS)**
- **ALCL, ALK+ small cell and histiocyte-rich variants**

Nodal localization (non-anaplastic morphology) → **Panel: CD2, CD3, CD4, CD5, CD7, CD8, CD30, ALK, CD10, BCL6, PD1/CD279, CXCL 13, CD21, CD23, EBV-EBER**

- **CD30+ ALK+** → **ALCL, ALK+ small cell or histiocyte-rich variants**
- **CD30+/- ALK-**
  - **CD10+ BCL6+ PD1+ CD4+/- CXCL 13+** →
    - **Vascular proliferation, expanded CD21+ CD23+ FDC = AITL**
    - **Nodular CD21+ CD23+ FDC = Follicular PTCL**
  - **CD10- BCL6-**
    - **HTLV1+ = ATLL (CD2+ CD5+ CD7- CD25+ CD56-)**
    - **HTLV1- = PTCL, NOS**

Nodal localization
- **Adult T-cell leukemia/lymphoma (ATLL)**
- **Angioimmunoblastic T-cell lymphoma (AITL)**
- **Peripheral T-cell lymphoma, NOS (PTCL, NOS)**
- **ALCL, ALK+ small cell and histiocyte-rich variants**

[a] These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.

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

Table 1: Classification of T-Cell Lymphomas

WHO Classification of the Mature T-Cell, and NK-Cell Neoplasms (2017)	The International Consensus Classification (ICC) of Mature Lymphoid Neoplasms (2022)	WHO Classification of Hematolymphoid Tumors: Lymphoid Neoplasms (5th edition, 2022)
Mature T-cell and NK-cell neoplasms	**Mature T-cell and NK-cell neoplasms**	**Mature T-cell and NK-cell neoplasms**
T-cell prolymphocytic leukemia	T-cell prolymphocytic leukemia	T-prolymphocytic leukaemia
T-cell large granular lymphocytic leukemia	T-cell large granular lymphocytic leukemia	T-large granular lymphocytic leukaemia
*Chronic lymphoproliferative disorder of NK-cells**	*Chronic lymphoproliferative disorder of NK cells*	NK-large granular lymphocytic leukaemia
Aggressive NK-cell leukemia	Aggressive NK cell leukemia	Aggressive NK-cell leukaemia
Adult T-cell leukemia/lymphoma	Adult T-cell leukemia/lymphoma	Adult T-cell leukaemia/lymphoma
Not previously included	*Primary nodal EBV-positive T-cell/NK-cell lymphoma**	EBV-positive NK-cell and T-cell lymphomas • EBV-positive nodal T- and NK-cell lymphoma
Extranodal NK/T-cell lymphoma, nasal type	Extranodal NK/T-cell lymphoma, nasal type	• Extranodal NK/T-cell lymphoma
Enteropathy-associated T-cell lymphoma	Enteropathy-associated T-cell lymphoma • Type II refractory celiac disease	Intestinal T-cell and NK-cell lymphoid proliferations and lymphomas • Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma*	Monomorphic epitheliotropic intestinal T-cell lymphoma	• Monomorphic epitheliotropic intestinal T-cell lymphoma
Intestinal T-cell lymphoma, NOS	Intestinal T-cell lymphoma, NOS	• Intestinal T-cell lymphoma, NOS
*Indolent T-cell lymphoproliferative disorder of the GI tract**	Indolent clonal T-cell lymphoproliferative disorder of the GI tract	• Indolent T-cell lymphoma of the gastrointestinal tract
Not previously included	Indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract	• Indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract

*Provisional entities are listed in italics.

With permission, Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, ed. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th ed. Lyon: IARC; 2017.
The International Consensus Classification of Mature Lymphoid Neoplasms: A Report from the Clinical Advisory Committee. Blood 2022;140:1229-1253.
Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia 2022;36:1720-174.

Classification

Table 1: Classification of T-Cell Lymphomas

WHO Classification of the Mature T-Cell, and NK-Cell Neoplasms (2017)	The International Consensus Classification (ICC) of Mature Lymphoid Neoplasms (2022)	WHO Classification of Hematolymphoid Tumors: Lymphoid Neoplasms (5th edition, 2022)
Mature T-cell and NK-cell neoplasms	**Mature T-cell and NK-cell neoplasms**	**Mature T-cell and NK-cell neoplasms**
Hepatosplenic T-cell lymphoma	Hepatosplenic T-cell lymphoma	Hepatosplenic T-cell lymphoma
Peripheral T-cell lymphoma, NOS	Peripheral T-cell lymphoma, NOS	Peripheral T-cell lymphoma, NOS
	Follicular helper T-cell lymphoma (TFH Lymphoma)	Nodal T-follicular helper (TFH) cell lymphoma
Angioimmunoblastic T-cell lymphoma	Follicular helper T-cell lymphoma (TFH Lymphoma) • Follicular helper T-cell lymphoma, angioimmunoblastic type	Nodal T-follicular helper (TFH) cell lymphoma • Nodal TFH cell lymphoma, angioimmunoblastic-type
*Follicular T-cell lymphoma**	• Follicular helper T-cell lymphoma, follicular type	• Nodal TFH cell lymphoma, follicular-type
*Nodal peripheral T-cell lymphoma with TFH phenotype**	• Follicular helper T-cell lymphoma, NOS	• Nodal TFH cell lymphoma, NOS
Anaplastic large-cell lymphoma, ALK positive	Anaplastic large cell lymphoma, ALK-positive	Anaplastic large cell lymphoma • ALK-positive anaplastic large cell lymphoma
Anaplastic large-cell lymphoma, ALK negative	Anaplastic large cell lymphoma, ALK-negative	• ALK-negative anaplastic large cell lymphoma
*Breast implant–associated anaplastic large-cell lymphoma**	Breast implant-associated anaplastic large cell lymphoma	• Breast implant-associated anaplastic large cell lymphoma

*Provisional entities are listed in italics.

With permission, Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, ed. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th ed. Lyon: IARC; 2017.
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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.

ABBREVIATIONS

AITL	angioimmunoblastic T-cell lymphoma
ALC	absolute lymphocyte count
ALCL	anaplastic large cell lymphoma
ANC	absolute neutrophil count
ANKL	aggressive natural killer cell leukemia
ATLL	adult T-cell leukemia/ lymphoma
BIA-ALCL	breast implant-associated anaplastic large cell lymphoma
C/A/P	chest/abdominal/pelvic
CBC	complete blood count
CCRT	concurrent chemoradiation therapy
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CSF	cerebrospinal fluid
CTV	clinical target volume
DLBCL	diffuse large B-cell lymphoma
EATL	enteropathy-associated T-cell lymphoma
EBER	Epstein-Barr virus–encoded RNA
EBER-ISH	Epstein-Barr encoding region in situ hybridization
EBV	Epstein-Barr virus
ECOG	Eastern Cooperative Oncology Group
ENKL	extranodal natural killer (NK)/T-cell lymphoma
ENT	ear, nose, and throat
FDG	fluorodeoxyglucose
FISH	fluorescence in situ hybridization
FNA	fine-needle aspiration
FTCL	follicular T-cell lymphoma
GI	gastrointestinal
G6PD	glucose-6-phosphate dehydrogenase
GTV	gross tumor volume
GVHD	graft-versus-host disease
HCT	hematopoietic cell transplant
HTS	high-throughput sequencing
HDAC	histone deacetylase
H&P	history and physical
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HLH	hemophagocytic lymphohistiocytosis
HSTCL	hepatosplenic T-cell lymphoma
HTLV	human T-cell lymphotropic virus
ICRU	International Commission on Radiation Units and Measurements
IGRT	image-guided radiation therapy
IHC	immunohistochemistry
IMRT	intensity-modulated radiation therapy
IPI	International Prognostic Index
ISRT	involved-site radiation therapy
ITV	internal target volume
IVF	in vitro fertilization
JCV	John Cunningham virus

Continued

ABBREVIATIONS

LDH	lactate dehydrogenase
LGL	large granular lymphocytosis
LGLL	large granular lymphocytic lymphoma
LFT	liver function test
LPD	lymphoproliferative disorder
MEITL	monomorphic epitheliotropic intestinal T-cell lymphoma
MUGA	multigated acquisition
NGS	next-generation sequencing
NK	natural killer
NOS	not otherwise specified
OARs	organs at risk
PCR	polymerase chain reaction
PD	progressive disease
PINK	Prognostic Index of Natural Killer Lymphoma
PJP	pneumocystis jiroveci pneumonia
PML	progressive multifocal leukoencephalopathy
PTCL	peripheral T-cell lymphoma
PTV	planning target volume
RA	rheumatoid arthritis
RBC	red blood cell
SLE	systemic lupus erythematosus
TCR	T-cell antigen receptor
TFH	T-follicular helper
T-LGLL	T-cell large granular lymphocytic leukemia
TLS	tumor lysis syndrome
T-PLL	T-cell prolymphocytic leukemia
ULN	upper limit of normal
WBC	white blood cell

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) 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.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

NCCN Guidelines Version 4.2024
T-Cell Lymphomas

This discussion corresponds to the NCCN Guidelines for T-Cell Lymphomas. Last updated: May 28, 2024.

Discussion

Table of Contents

Overview

Non-Hodgkin lymphomas (NHLs) 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 2024, an estimated 80,620 people will be diagnosed with NHL and there will be approximately 20,140 deaths due to the disease.[1] In prospectively collected data from the National Cancer Data Base, diffuse large B-cell lymphoma (DLBCL; 32%), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL; 19%), follicular lymphoma (FL; 17%), marginal zone lymphoma (MZL; 8%), mantle cell lymphoma (MCL; 4%), and peripheral T-cell lymphoma not-otherwise-specified (PTCL-NOS; 2%) were the major subtypes of NHL diagnosed in the United States between 1998 and 2011.[2]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) 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® for T-Cell Lymphomas are listed below:

- Peripheral T-cell lymphomas (PTCL)
- Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL)
- T-cell large granular lymphocytic leukemia (TGLL)
- T-cell prolymphocytic leukemia (TPLL)
- Adult T-cell leukemia/lymphoma (ATLL)
- Hepatosplenic T-cell lymphoma (HSTCL)
- Extranodal NK/T-cell lymphomas (ENKL)

Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation. NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Classification

In 2022, in addition to the newly revised WHO Classification of Hematolymphoid Tumors (WHO5),[3] another new classification system known as International Consensus Classification (ICC) was also published.[4] While both the ICC and WHO5 continue to classify the lymphoid malignancies based on morphology, clinical features, cell lineage (immunophenotype), and cytogenetic and molecular features, there are differences between the two classifications in terms of nomenclature and diagnostic criteria. These are discussed under the respective subtypes of T-cell lymphomas.

Staging

PET/CT scans are now used 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.[5] 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.[6,7] 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.[6] 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.[7] PET/CT is particularly important for staging before consideration of radiation therapy (RT) and baseline PET/CT will aid in the interpretation of post-treatment response evaluation based on the 5-point scale (5-PS) as described above.[8]

PET/CT is recommended for initial staging of 18F-fluorodeoxyglucose (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.

Response Assessment

The guidelines for response criteria for lymphoma were first published in 1999 by the International Working Group (IWG).[9] These response criteria are based on the reduction in 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.[9] These guidelines were revised in 2007 by the International Harmonization Project to incorporate immunohistochemistry (IHC), flow cytometry, and PET scans in the definition of response for lymphoma.[10] In the revised guidelines, the response is categorized as complete response (CR), partial response (PR), stable disease (SD), and relapsed disease or progressive disease (PD) based on the result of a PET scan. The response category of complete response uncertain (CRu) was essentially eliminated.

In 2014, revised response criteria, known as the Lugano criteria, were introduced for response assessment using PET/CT scans according to the 5-PS.[8,11] 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.[12-14] 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, but a score of 1 to 3 is now widely considered to be PET negative. Scores of 4 to 5 are universally considered PET 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 FDG-avid lymphomas and the revised response criteria have thus far only been validated for DLBCL and Hodgkin lymphoma. The application of the revised response criteria to other histologies requires validation and the original IWG guidelines should be used. 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

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, 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 greater than or equal to 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. Recommendations for normal tissue dose constraints can be found in the *Principles of Radiation Therapy* section of the NCCN Guidelines for Hodgkin Lymphoma.

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 disintegration of malignant cells by anticancer therapy and rapid release of intracellular contents into peripheral blood. It is usually observed within 12 to 72 hours after start of chemotherapy.[20]

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. Hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia are the primary electrolyte abnormalities associated with TLS. Clinical symptoms may include nausea and vomiting, diarrhea, seizures, shortness of breath, renal insufficiency, or cardiac arrhythmias. Untreated TLS can induce profound metabolic changes resulting in cardiac arrhythmias, seizures, loss of muscle control, acute renal failure, and even death. The cornerstone of TLS management is hydration and the management of hyperuricemia. Allopurinol, febuxostat, and rasburicase are highly effective for the management of hyperuricemia.

Allopurinol is a xanthine analog and a competitive inhibitor of xanthine oxidase, thereby blocking the conversion of purine metabolites to uric acid and decreasing the formation of uric acid production.[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 allopurinol, which may delay the start of chemoimmunotherapy. 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, a recombinant urate oxidase, 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.[23-25] In a prospective, multicenter, randomized phase III trial of adult patients with hematologic malignancies at high or potential risk for TLS (275 patients; rasburicase alone, n = 92; rasburicase combined with allopurinol, n = 92; allopurinol alone, [n = 91), 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%; $P = .015$).[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 ($P = .003$). 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.

There are data to suggest that single fixed dose (6 mg or 3 mg) or single weight-based dose of rasburicase (0.05–0.15 mg/kg) are effective in adult patients with hyperuricemia or high-risk factors for TLS.[26-31] In the phase II randomized trial that 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 80 adult patients at high risk or potential risk for TLS, 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.[31] The median pretreatment uric acid level was 8.5 mg/dL for patients at high risk for TLS (n = 40) and 5.6 mg/dL for patients at potential risk for TLS (n = 40). 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 patients with high-risk disease within the single-dose arm, 6 patients received a second dose of rasburicase to achieve uric acid response.

In a randomized trial that compared the efficacy and safety of febuxostat and allopurinol in 346 adult patients with hematologic malignancies at intermediate or high risk for TLS, one fixed dose of febuxostat achieved a significantly superior serum uric acid control in comparison to allopurinol with comparable renal function preservation and safety profile.[32]

TLS is best managed if anticipated and when treatment is started prior to chemoimmunotherapy. Histologies of Burkitt lymphoma (BL), lymphoblastic lymphoma and occasionally DLBCL, bone marrow involvement, bulky tumors that are chemosensitive, rapidly proliferative or aggressive hematologic malignancies, an elevated leukocyte count or pretreatment lactate dehydrogenase (LDH), pre-existing elevated uric acid, renal disease, or renal involvement of tumor are considered as risk factors for developing TLS.[33] TLS prophylaxis should be considered for patients with any of these risk factors. Frequent monitoring of electrolytes and aggressive correction are essential.

Allopurinol or febuxostat is recommended for patients with low-risk or intermediate-risk disease. Rasburicase is recommended for intermediate-risk disease (if renal dysfunction and uric acid, potassium, and/or phosphate greater than upper limit of normal [ULN]) or high-risk disease. Allopurinol and febuxostat should be started 2 to 3 days prior to the initiation of chemotherapy and continued for 10 to 14 days. A single dose of rasburicase (3 mg or 6 mg) is adequate in most circumstances and repeat dosing should be individualized based on the presence of any of the following risk factors: bulky disease requiring immediate therapy; adequate hydration is not possible; or acute renal failure. Rasburicase is contraindicated in patients with G6PD deficiency due to an increased risk of methemoglobinemia or hemolysis.[34] G6PD testing should be considered prior to the initiation of rasburicase. Rasburicase should be substituted with allopurinol G6PD deficiency.

Viral Reactivation and Infections

Cytomegalovirus Reactivation

Cytomegalovirus (CMV) reactivation is a well-documented infectious complication in patients receiving treatment with alemtuzumab, occurring in up to 25% of treated patients. CMV reactivation may occur among patients with hematologic malignancies treated with alemtuzumab containing regimens, most frequently between 3 to 6 weeks after initiation of therapy when T-cell counts reach a nadir. The panel recommends measurement of CMV viremia using quantitative polymerase chain reaction (PCR) at least every 2 to 3 weeks during the treatment course with alemtuzumab and for 2 months following completion of alemtuzumab treatment. Current management practices for the prevention of CMV reactivation include the use of prophylactic ganciclovir prior to alemtuzumab therapy if CMV viremia is present, or preemptive use of

these drugs when the viral load is found to be increasing during therapy. Evaluation of CD52 expression should be considered before initiating treatment with alemtuzumab-based regimens.

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 John Cunningham (JC) polyomavirus. Patients with NHL receiving treatment with the anti-CD30 antibody-drug conjugate brentuximab vedotin may be at potential risk for PML.[35] 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.[35] 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.

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Peripheral T-Cell Lymphomas

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of lymphoproliferative disorders arising from mature T cells, accounting for about 10% of non-Hodgkin lymphomas (NHLs). PTCL-not otherwise specified (PTCL-NOS; 26%) is the most common subtype, followed by angioimmunoblastic T-cell lymphoma (AITL; 19%), anaplastic large cell lymphoma (ALCL), anaplastic lymphoma kinase (ALK)-positive (7%), ALCL, ALK-negative (6%), and enteropathy-associated T-cell lymphoma (EATL; <5%).[1]

PTCL-NOS most often involves nodal sites; however, many patients present with extranodal involvement, including the liver, bone marrow, gastrointestinal (GI) tract, and skin. PTCL-NOS is associated with poorer overall survival (OS) and event-free survival (EFS) rates compared to aggressive B-cell lymphomas.[2,3] Gene expression profiling (GEP) studies and immunohistochemistry (IHC) algorithms have identified two major molecular subgroups of PTCL-NOS (characterized by high expression of either GATA3 or TBX21).[4-7] In a multivariate analysis, a high international prognostic index (IPI) score and PTCL-GATA3 subtype identified by IHC were independently associated with poor OS.[7] The 2022 WHO classification (WHO5) and International Consensus Classification (ICC) also recognize the clinical significance of GATA3 and TBX21 expression in PTCL-NOS subtypes.[8,9]

AITL occurs mainly in older patients with a prognosis similar to PTCL-NOS and usually presents with generalized lymphadenopathy, and is often with associated hypergammaglobulinemia, hepatomegaly or splenomegaly, eosinophilia, skin rash, and fever.[3,10,11] AITL is also characterized by the frequent presence of Epstein-Barr virus (EBV)-positive B-cells and cases of AITL coexistent EBV+ diffuse large B-cell lymphoma (DLBCL) are reported.[11-13]

Nodal T-cell lymphomas of T-follicular helper (TFH) cell origin have a more favorable prognosis and also respond better to certain therapies, particularly therapies targeting epigenetics, such as histone deacetylase (HDAC) inhibitors when compared with other PTCL subtypes.[14-16] Nodal T-cell lymphomas of TFH phenotype express TFH cell markers (eg, CD10, BCL6, CXCL13, PD1, ICOS) and recurrent mutations in *TET2, DNMT3A*, *IDH2,* and *RHOA*G17V genes have been identified in the majority of cases.[17-20] In the 2017 WHO classification, the category of nodal lymphomas of TFH cell origin was created to include the three subtypes: AITL, PTCL with TFH phenotype, and follicular helper T-cell lymphoma.[21] In WHO5, all three subtypes of nodal lymphomas of TFH cell origin are listed under a new category, nodal TFH cell lymphomas and are renamed as nodal TFH cell lymphoma, angioimmunoblastic-type, nodal TFH cell lymphoma, NOS and nodal TFH cell lymphoma, follicular-type, respectively.[8] In the ICC, follicular helper T-cell lymphoma is considered as a single entity encompassing the three subtypes (follicular helper T-cell lymphoma, angioimmunoblastic type, follicular helper T-cell lymphoma, follicular type and follicular helper T-cell lymphoma, NOS).[9]

ALCL is a CD30-expressing subtype that accounts for less than 5% of all cases of NHL. There are now four distinctly recognized subtypes of ALCL: systemic ALCL, ALK-positive; systemic ALCL, ALK-negative; breast implant-associated ALCL (BIA-ALCL), and primary cutaneous ALCL. BIA-ALCL represents a distinct entity from systemic ALCL and other forms of primary breast lymphoma (which are usually of B-cell origin).[8,9]

ALCL, ALK-positive is most common in children and young adults and is characterized by the overexpression of ALK-1 protein, resulting from a chromosomal translocation [t(2;5)] in 40% to 60% of patients.[22] The majority of patients with systemic ALCL present with advanced stage III or IV disease (65% for ALK-positive and 58% for ALK-negative) frequently associated with systemic symptoms and extranodal involvement.[23]

IHC, FISH, and GEP studies have identified molecular subtypes of ALCL, ALK-negative characterized by the presence of dual-specificity phosphatase 22 (*DUSP22*) and *TP63* rearrangements.[24-29] In earlier reports, the presence of *DUSP22* rearrangement (identified in 30% of all ALCL, ALK-negative cases) was associated with a favorable prognosis (5-year OS rate, 80%–90%), whereas the presence of *TP63* rearrangement (occurring in about 8% of cases) was associated with a worse prognosis (5-year OS rate of 17%).[24,25] Other studies have reported that ALCL, ALK-negative with a *DUSP22* rearrangement is not associated with better clinical outcome and cases with *DUSP22* rearrangement were also associated with some high-risk features (probably contributing to lower survival outcome).[27,28] Nevertheless, outcomes in the presence of *DUSP22* rearrangement were significantly better than both ALCL, ALK-negative with *TP63* rearrangements and triple negative ALCL lacking all 3 rearrangements of *ALK, DUSP22*, and *TP63*.[27,29] In a retrospective study of the Lymphoma Study Association (LYSA), which analyzed the outcomes of 104 patients with ALCL, ALK-negative based on the *DUSP22* status, after a median follow-up of 5 years, the 5-year progression-free survival (PFS) rate was 57% for patients with *DUSP22* rearrangement compared to 26% for those with triple negative ALCL.[29] The corresponding 5-year OS rates were 65% and 41%, respectively.

EATL is a rare T-cell lymphoma of the small intestine, accounting for less than 1% of all NHLs, and is associated with a very poor prognosis.[30-33] The median age of diagnosis is 60 years. In the previous WHO classifications, EATLs were classified as EATL type I and EATL type II, but only EATL type I was truly associated with enteropathy (celiac disease). In the 2017 WHO classification, the two diseases were redefined as separate entities. EATL type 1 (associated with celiac disease) was defined as EATL and EATL type II was renamed as monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL).[21] In WHO5, both EATL and MEITL are listed under intestinal T-cell and NK-cell lymphoid proliferations and lymphomas.[8] In the analysis from the International T-Cell Lymphoma Project, EATL comprised 5% of all PTCL and natural killer (NK)-cell lymphomas included in the study.[33] EATL was more common (66%) than MEITL (34%). With a median follow-up of 11 months, the median OS and failure-free survival (FFS) were 10 months and 6 months for EATL and MEITL, respectively. The 5-year OS and FFS rates were 20% and 4%, respectively. The optimal treatment for MEITL has not yet been defined.

Literature Search Criteria

Prior to the update of this version of the NCCN Clinical Practice Guidelines (NCCN Guidelines®) for T-Cell Lymphomas an electronic search of the PubMed database was performed to obtain key literature in peripheral T-cell lymphomas published since the last Guidelines update. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[34]

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 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.

Prognosis

PTCLs carry a poorer prognosis than aggressive B-cell lymphomas since they are less responsive to and have less frequent durable remissions with

standard anthracycline-based chemotherapy regimens. Progress has been further hampered by the relative rarity and the biological heterogeneity. In general, ALCL, ALK-positive is associated with better clinical outcomes than ALCL, ALK-negative, PTCL-NOS, or AITL. The favorable prognosis of ALK-1 positivity, however, is diminished with older age and higher prognostic risk scores.[35-39] In an analysis of 341 patients with newly diagnosed PTCL treated with anthracycline-based chemotherapy, the 3-year PFS and OS rates (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 hematopoietic cell transplant (HCT).[38] 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.

In the survival analysis from the International T-Cell Lymphoma Project, ALCL, ALK-positive was associated with significantly better prognosis with anthracycline-containing regimens compared with ALCL, ALK-negative, both in terms of the 5-year FFS rate (60% vs. 36%; *P* = .015) and OS rate (70% vs. 49%; *P* = .016). ALCL, ALK-negative was associated with superior survival rates when compared with PTCL-NOS (5-year FFS and OS rates were 20% and 32%, respectively).[36]

In a 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.[10] The corresponding EFS rates were 29% and 23%, respectively. In the recently published survival analyses from the International T-Cell Lymphoma Project, 5-year PFS and OS rates were 43% and 49%, respectively, for patients with ALCL, ALK-negative treated with multiagent chemotherapy regimens and the estimated 5-year PFS and OS rates were 32% and 44%, respectively, for patients with AITL.[40,41] A novel prognostic score (AITL score) based on age (age ≥60 years; ECOG PS >2; elevated C-reactive protein and elevated β2 microglobulin) stratified patients into three risk groups (low-, intermediate-, and high-risk) with estimated 5-year OS rates of 63%, 54%, and 21%, respectively.[41]

Historically, the IPI and NCCN-IPI developed for DLBCL have been used for the risk stratification of patients with PTCL.[2,23,42] Prognostic Index for PTCL-U (PIT) and T-cell score are the new prognostic models that have been developed for the risk stratification of patients with PTCL-NOS.[43,44] PIT is based on the following risk factors: age >60 years, elevated lactate dehydrogenase (LDH) levels, performance status of 2 or more, and bone marrow involvement.[43] The 5-year OS rate was 33% for patients with two risk factors and 18% for those with three or four risk factors. This prognostic index also identified a subset of patients with relatively favorable prognosis who had no adverse risk factors.[43] This group represented 20% of patients and had a 5-year OS rate of 62%. T-cell score (developed by the International T-cell Project Network) is based on four clinical variables: serum albumin, performance status, stage, and absolute neutrophil count. T-cell score stratified patients into three risk groups (low-, intermediate-, and high-risk) with estimated 3-year OS rates of 76%, 43%, and 11%, respectively.[44]

In a pooled analysis of three international cohorts of nodal PTCL, all three indices (IPI, NCCN-IPI, and PIT) demonstrated better risk stratification for ALK-ALCL and PTCL-NOS.[45] However, none of the indices was useful for prognostication or stratification in AITL. IPI, NCCN-IPI, and PIT can be used to stratify for prognosis and under certain circumstances may aid in guiding treatment decisions for patients with PTCL.

Progression of disease within 24 months (POD24) after primary treatment has been identified as a predictor of survival in patients with newly diagnosed PTCL. In a large multinational cohort study of 775 patients with

newly diagnosed PTCL, the median OS was 5 months versus not reached for those without POD24.[46] The corresponding 5-year OS rates were 11% and 78%, respectively. The prognostic significance of POD24 in patients with newly diagnosed PTCL was also demonstrated in subsequent studies.[41,47-49] These results suggest that patients with primary refractory disease or early relapse have extremely poor survival and that POD24 could be used for risk stratification of patients with PTCL.

Diagnosis

Excisional or incisional biopsy is preferred over core needle biopsy if possible for initial diagnosis. If only core needle biopsy is feasible due to the sites of disease, a combination of core needle biopsy and fine-needle aspiration (FNA) biopsy in conjunction with appropriate ancillary techniques may be sufficient for diagnosis (multiple cores should be obtained to allow for adequate workup).

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). While CD30 expression can be found at times in many T-cell lymphomas, with the exception of systemic ALCL (which has a uniform strong expression of CD30), CD30 expression by IHC (score of ≥2) is variable across other subtypes of PTCL (52% in PTCL-NOS and 21% in AITL).[50] The majority of the nodal cases express CD4 and lack CD8; however, CD4-/CD8+, CD4-/CD8-, and CD4+/CD8+ cases are seen.[51] 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.[52,53]

Adequate immunophenotyping is essential to distinguish PTCL subtypes from B-cell lymphomas. The initial paraffin panel for IHC studies may only include pan–T-cell markers and can be expanded to include antibodies of T-cell lymphoma, if suspected. The IHC panel may include the following markers: CD20, CD3, CD10, BCL6, Ki-67, CD5, CD30, CD2, CD4, CD8, CD7, CD56, CD21, CD23, TCRβ, TCRδ, PD1/CD279, ALK, and TP63. Alternatively, the following markers can be analyzed by flow cytometry: CD45, CD3, CD5, CD19, CD10, CD20, CD30, CD4, CD8, CD7, and CD2; and TCRα, TCRβ, and TCRγ. As noted earlier, AITL may occasionally present with concurrent EBV+ DLBCL and EBV evaluation by Epstein-Barr encoding region in situ hybridization (EBER-ISH) should be performed.[11-13]

IHC for ALK1 or molecular analysis to detect t(2;5) or variant translocations, is essential to identify ALCL, ALK-positive that has a better prognosis. IHC for markers of TFH cell origin (CXCL13, ICOS, PD1) are recommended if PTCL-NOS or TFH phenotype is suspected. The use of next-generation sequencing (NGS) panel may also be useful to support the diagnosis of TFH subtypes. IHC for cytotoxic T-cell markers (TIA-1, granzyme B, perforin) may be useful to characterize subsets of PTCL.[17,52,53]

PTCL is often associated with clonal T-cell antigen receptor (*TCR*) gene rearrangements that are less frequently seen in non-cancer T-cell diseases. Molecular analysis to detect clonal *TCR* gene rearrangements is useful for the assessment of T-cell clonality although false-positive results or non-malignant clones can at times be identified. TRBC1 expression by flow cytometry has been reported as a highly sensitive method for the assessment of T-cell clonality with good correlation with molecular methods.[54-57]

Molecular analysis to detect t(2;5) translocations involving the *ALK* gene may be useful for patients with ALCL, ALK-positive and molecular analysis to detect *DUSP22* rearrangement and *TP63* rearrangement (if IHC is positive for TP63) may be useful for patients with ALCL, ALK-negative. As discussed earlier, ALCL, ALK-negative with *DUSP22* rearrangement is associated with a favorable prognosis more similar to ALK-positive

ALCL, although the data supporting a truly favorable prognosis is inconsistent, whereas ALCL, ALK-negative with *TP63* rearrangements and triple negative ALCL (lacking all 3 rearrangements of *ALK, DUSP22*, and *TP63)* are associated with an unfavorable prognosis (inferior survival outcomes compared to ALCL, ALK-negative with *DUSP22* rearrangement).[24-29]

Workup

The workup for PTCL is similar to the workup for other lymphoid neoplasms, focusing on the determination of stage, routine laboratory studies (bone marrow biopsy ± aspirate, complete blood count [CBC] with differential, comprehensive metabolic panel), physical examination including a full skin exam, and imaging studies, as indicated. PET/CT scan and/or chest/abdomen/pelvis (C/A/P) CT with contrast of diagnostic quality are essential during workup. In some cases, CT scan of the neck and CT or MRI of the head may be useful. Multigated acquisition (MUGA) scan or echocardiogram is also recommended since chemotherapy is usually anthracycline based.

In selected cases, serology testing for the human immunodeficiency virus (HIV) and human T-cell lymphotropic virus (HTLV-1) may be useful. HTLV-1 positivity, in particular, can lead to the alternate diagnosis and alternate management of adult T-cell leukemia/lymphoma (ATLL) for cases that would otherwise be classified as PTCL-NOS by the pathologist if positive HTLV-1 serology was not known.

First-line Therapy

In prospective randomized studies, PTCLs have been included with aggressive B-cell lymphomas and it has not been possible to assess the impact of chemotherapy in the subgroup of patients with PTCLs due to small sample size. Data to support the use of multiagent combination chemotherapy for the treatment of previously untreated PTCL are available mainly from retrospective analyses and small prospective studies (as discussed below).

Anthracycline-based chemotherapy regimens (eg, CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone] or CHOP + etoposide [CHOEP] or dose-adjusted EPOCH [etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin]) are the most commonly used first-line therapy regimens since these are associated with a trend toward significance in mortality reduction.[58] However, with the exception of ALK+ ALCL, outcomes are not optimal in other subtypes.[3,59-63]

In a retrospective analysis of 289 patients with PTCL treated within the DSHNHL trials, CHOEP was associated with an event-free survival benefit in ALCL, ALK-positive in patients <60 to 65 years of age and also in patients with subtypes other than ALCL, ALK-positive with low-risk IPI (IPI <1).[60] The Nordic Lymphoma Group also reported similar findings among 122 patients with ALCL, ALK-positive treated with the CHOEP regimen (5-year OS and PFS rates were 78% and 64%, respectively).[61] CHOEP regimen was associated with an improved OS in patients aged 41 to 65 years, even after adjusting for risk factors (P = .05). Bone marrow involvement was independently associated with poorer PFS in a multivariate analysis.

In a prospective study of 24 patients with previously untreated ALCL, with a median follow-up of 14 years, dose-adjusted EPOCH resulted in the EFS rates of 72% and 63% (P = .54), respectively, for patients with ALCL, ALK-positive and ALCL, ALK-negative and the OS rates were 78% and 88% (P = .83), respectively.[62] However, definitive conclusions from these findings are limited by the small number of patients and possible selection bias (24 patients recruited over 16 years; median patient age was 36 years for ALCL, ALK-positive and 43 for ALCL, ALK-negative). In another prospective study from Japan that evaluated dose-adjusted EPOCH as initial therapy in 41 patients with PTCL (PTCL-NOS was the

predominant subtype [n = 21, 51%] followed by AITL [n = 17, 42%]), the overall response rate (ORR) and complete response (CR) rate were 78% and 61%, respectively.[63] At a median follow-up of 24 months, the 2-year PFS and OS rates were 53% and 73%, respectively. The ORR, CR, PFS, and OS rates were higher among patients ≤60 years of age (94%, 71%, 63%, and 82%, respectively).

The use of more intensive chemotherapy regimens also has not resulted in favorable outcomes in patients with PTCL, with the exception of ALCL. In a retrospective analysis that compared CHOP with more intensive chemotherapy regimens, including hyper-CVAD (hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and prednisone) in 135 patients with T-cell malignancies (PTCL-NOS, n = 50; ALCL, n = 40; AITL, n = 14), there was a trend towards higher 3-year OS rate for patients with ALK-positive ALCL treated with hyper-CVAD regimen compared to those with ALCL, ALK-negative (100% vs. 70%, respectively).[64] When the subgroup with ALCL was excluded from the analysis, the 3-year OS rate with CHOP and intensive regimen were 43% and 49%, respectively.

Results from more recent studies also suggest that the addition of anti-CD52 monoclonal antibody (alemtuzumab) or histone deacetylase (HDAC) inhibitor or lenalidomide to CHOP or CHOEP did not improve survival, at least in part due to increased toxicity.[65-69] The phase III trial comparing romidepsin + CHOP versus CHOP excluded patients with ALK-positive, ALCL did not show a statistically significant PFS benefit for romidepsin + CHOP in the entire study population (hazard ratio [HR], 0.81; 95% CI, 0.63–1.04; *P* = .096).[67] However, an exploratory analysis suggests a PFS benefit for romidepsin + CHOP in a subgroup of patients with histologically confirmed PTCL with TFH phenotype (20 months vs. 11 months for CHOP).[66] Although statistical considerations preclude any firm conclusion, these findings are consistent with other reports that have suggested HDAC inhibitors may have superior activity in nodal TFH cell lymphomas compared with other PTCL subtypes.[14,15] The addition of azacitidine to CHOP has also been shown to induce high CR rate in PTCL with TFH phenotype and this combination will be further evaluated in a randomized study.[70]

The phase III randomized trial (ECHELON-2) showed that brentuximab vedotin (BV) in combination with CHP (cyclophosphamide, doxorubicin, and prednisone) was superior to CHOP for the treatment of patients with previously untreated CD30-positive PTCL (defined in ECHELON-2 as CD30 expression on ≥10% of cells), resulting in significantly improved PFS and OS.[71,72] In this trial, 452 patients were randomly assigned to either BV + CHP or CHOP and the majority (70%) of patients had ALCL (48% ALCL, ALK-negative and 22% ALCL, ALK-positive). After a median follow-up of 48 months, the median PFS was 62 months and 24 months for BV + CHP and CHOP, respectively. The estimated 5-year PFS rates were 51% and 43% for BV + CHP and CHOP, respectively.[72] The median OS was not reached in either arm and the estimated 5-year OS rates were 70% and 61% for BV + CHP and CHOP, respectively. The ORR (83% vs. 72%) and CR rate (68% vs. 56%) were also higher for BV + CHP compared to CHOP. The estimated 5-year PFS rates were 61% for BV + CHP vs. 48% for CHOP in the subset of patients with ALCL (HR, 0.55; HR, 0.40 for ALK-positive and HR, 0.58 for ALK-negative). The estimated 5-year OS rates were 76% for BV + CHP and 69% for CHOP in the subset of patients with ALCL (HR, 0.66; HR, 0.48 for ALK-positive and HR, 0.71 for ALK-negative). The survival benefit (clearly established for the subset of patients with ALCL) was less clear across other histological subtypes (the HR for PFS and OS were 0.79 and 0.75, respectively, for PTCL-NOS and the corresponding HRs were 1.4 and 1.0, respectively, for AITL), all with wide confidence intervals.[72] However, this study was not powered to compare efficacy of BV + CHP within individual histologic subtypes due to small subgroup sizes.

Neutropenia (35%), anemia (13%), diarrhea (6%), peripheral neuropathy (4%), and nausea (2%) were the most common grade ≥3 adverse events with BV + CHP. Peripheral neuropathy associated with BV continued to improve or resolve with long-term follow-up. Based on the results of the ECHELON-2 trial, BV in combination with CHP was approved by the U.S. Food and Drug Administration (FDA) as a first-line therapy for patients with untreated systemic ALCL or other CD30-expressing subtypes (≥1% CD30 expression) including PTCL-NOS and AITL.

NCCN Recommendations

Multiagent chemotherapy (6 cycles with or without involved-site radiation therapy [ISRT] or for 3 to 4 cycles with ISRT) is recommended for patients with stage I,II ALCL, ALK-positive. Multiagent chemotherapy alone for 6 cycles is recommended for patients with stage III–IV ALCL, ALK-positive.

Participation in clinical trials is the preferred management approach for patients with other subtypes (PTCL-NOS, ALCL, ALK-negative, EATL, MEITL, and nodal TFH cell lymphomas). In the absence of suitable clinical trials, multiagent chemotherapy (6 cycles) with or without ISRT is recommended for all patients (stage I–IV disease). ALK-negative with a *DUSP22* rearrangement has been variably associated with a prognosis more similar to ALK-positive ALCL and could be treated according to the algorithm for ALCL, ALK-positive.[24-29]

Based on results of the ECHELON-2 trial and FDA approval, BV + CHP is included as a preferred first-line therapy option for patients with ALCL (category 1) or other CD30-positive histologies (category 2A). CHOP, CHOEP, dose-adjusted EPOCH, or hyper-CVAD are included as other options for multiagent chemotherapy. As noted earlier, CD30 expression is variable across the PTCL subtypes other than ALCL.[50] Interpretation of CD30 expression is not universally standardized. In the ECHELON-2 study, CD30 expression level did not correlate with response, in histologies other than ALCL and responses with BV have been observed in patients with all levels of CD30 expression, including in patients with very low or absent CD30 expression.[72,73]

CHOP followed by IVE (ifosfamide, etoposide, and epirubicin) alternating with intermediate-dose methotrexate (MTX) as initial therapy resulted in a median PFS and OS of 3 months and 7 months, respectively, in patients with EATL.[74] The 5-year PFS and OS rates (52% and 60%, respectively) were significantly higher in historical comparison with the corresponding survival rates (5-year PFS and OS rates were 22%) reported with conventional anthracycline-based chemotherapy regimens. CHOP followed by IVE alternating with MTX may be an appropriate first-line therapy option for patients with EATL.

First-line Consolidation Therapy

Several non-randomized prospective studies[74-85] and retrospective analyses[86-90] have reported favorable outcomes in patients with PTCL undergoing first-line consolidation with autologous HCT. Some studies have reported that the achievement of CR to first-line therapy is an independent predictor of improved survival in patients receiving first-line consolidation with autologous HCT.[76,80,89,91]

A report from Comprehensive Oncology Measures for Peripheral T-Cell Lymphoma Treatment (COMPLETE), a prospective multicenter cohort study, suggests that consolidation of first complete remission (CR1) with HDT/ASCR may provide a survival benefit in selected patients with PTCL (eg, patients with advanced-stage disease or intermediate-to-high IPI scores).[92] Consolidation with autologous HCT significantly improved OS and PFS for patients with AITL but not for patients with other PTCL subtypes.

In a randomized phase III study that evaluated the role of autologous versus allogeneic HCT following an anthracycline-based induction therapy in patients with high-risk nodal PTCL, the EFS and OS outcomes

were similar for patients in both treatment arms.[93] With a median follow-up of 42 months, the 3-year EFS rates were 43% and 38%, respectively, for patients randomized to allogenic HCT and autologous HCT. The corresponding 3-year OS rates were 57% and 70%, respectively. However, autologous HCT was associated with a much higher relapse rate (36% vs. 0%) and allogeneic HCT resulted in much higher transplant-related mortality (31% vs. 0%).

In the ECHELON-2 trial, first-line consolidation with HCT was permitted (at investigator's discretion). After a median follow-up of 48 months, the median PFS was not reached for those who underwent consolidation with HCT compared to 56 months for those who did not undergo HCT.[94] The PFS benefit with HCT was seen both in ALCL, ALK-negative group and in non-ALCL group. In the aforementioned analysis from the International T-Cell Lymphoma Project, consolidation with autologous HCT following CR to first-line therapy was associated with improved outcomes in patients with AITL.[41]

There is however no definitive study on the benefits of HCT as consolidation of first remission with other retrospective studies showing no survival advantage for patients PTCL-NOS, AITL, or ALCL, ALK-negative.[95-97]

In the absence of data from randomized controlled trials, available evidence (as discussed above) suggests that autologous HCT is a reasonable treatment option only in patients with disease responding to induction therapy (although it is associated with a high relapse rate).[92-94] Longer follow-up and preferably data from a prospective randomized trial are necessary to evaluate the impact of first-line consolidation therapy with autologous HCT on time-to-treatment failure and OS outcomes.

Response Assessment and Additional Therapy

Recent studies that have evaluated the utility of PET scans for assessment of response to therapy suggest that a positive interim PET scan after first- or second-line therapy for relapsed/refractory disease is an independent predictor of survival outcomes, thus suggesting that the use of interim PET scans may be helpful for risk stratification and could be used for risk-adapted treatment approach in patients with PTCL.[98-104] However, the optimal use of interim PET scans for the evaluation of response to treatment has not yet been established in a prospective study.

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.[105-107] 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 PET-positive. A score of 4 on an interim or end-of-treatment restaging scan may be consistent with a partial response (PR) if the FDG avidity has declined from initial staging, while a score of 5 denotes progression of disease.

The guidelines recommend interim restaging with PET/CT (preferred) or CT after 3 to 4 cycles of chemotherapy. Completion of planned course of treatment followed by end-of treatment restaging is recommended for all patients achieving CR or PR to first-line therapy. Patients with no response or progressive disease after initial therapy should be treated as outlined for relapsed or refractory disease.

Patients with a CR at end of treatment can either be observed or treated with first-line consolidation with autologous HCT. First-line consolidation should be considered for all patients with subtypes other than ALCL, ALK-positive. Among patients with ALCL, ALK-positive, first-line consolidation should be considered only for patients with high-risk IPI.

Localized areas can be treated with RT before or after autologous HCT. Rebiopsy should be considered (especially for patients with AITL since it may occasionally present with concurrent DLBCL) prior to addition therapy for patients with PR (persistent or new PET-positive lesions) at end-of-treatment restaging.

Treatment for Relapsed or Refractory Disease

Autologous[108-114] and allogeneic HCT[112,113,115-120] have only been evaluated in retrospective studies in patients with relapsed or refractory PTCL-NOS.

The general conclusion from these studies is that autologous HCT less frequently results in durable benefit in patients with relapsed or refractory disease as compared to allogeneic HCT. However, this conclusion is not universal in the literature and autologous HCT has been associated with a survival benefit more often in patients with ALCL subtype and chemosensitive disease than in those with non-ALCL subtypes and less chemosensitive disease.[108,110,112] The cumulative incidence of non-relapse mortality (NRM) was also higher with allogeneic HCT compared with autologous HCT.[112] Allogeneic HCT 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.[115-118] Further data from prospective studies are needed to determine the role of autologous and allogeneic HCT in patients with relapsed/refractory PTCL.

Second-line therapy for relapsed/refractory disease remains suboptimal, even with the incorporation of autologous or allogeneic HCT. Among the 420 evaluable patients with relapsed and refractory PTCL from the COMPLETE registry, outcomes were inferior for patients with refractory disease compared to those with relapsed disease.[121] The median OS was 29 months and 12 months, respectively, for patients with relapsed and refractory disease. 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 relapsed/refractory disease depends largely on the patient's eligibility for transplant.

Second-line systemic therapy followed by consolidation with autologous or allogeneic HCT 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 ISRT before or after autologous HCT. Allogeneic HCT, when feasible, should be considered for the majority of patients with relapsed/refractory disease. Autologous HCT may be an appropriate option, 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 radiation therapy (RT).

Data from clinical trials supporting the use of second-line systemic therapy options recommended in the guidelines are discussed below.

Bendamustine

In a multicenter phase II study (BENTLEY trial) of heavily pretreated patients with relapsed or refractory PTCL (n = 60; AITL, 53%; PTCL-NOS, 38%), bendamustine resulted in an ORR of 50% (28% CR) and the median duration of response was only 3.5 months.[122] Response rates were higher in patients with AITL compared to those with other subtypes. The ORR for AITL and PTCL-NOS was 69% and 41%, respectively (P = .47). However, this study was not powered to show differences in response rates between the different histologic subtypes. The median PFS and OS for all patients were 4 months and 6 months, respectively. The most common grade 3 or 4 toxicity included neutropenia (30%), thrombocytopenia (24%), and infectious events (20%).

Brentuximab Vedotin

The safety and efficacy of BV (an antibody-drug conjugate that targets CD30-expressing malignant cells) in patients with relapsed or refractory systemic ALCL was initially established in a multicenter phase II study.[123] Long-term follow-up results confirmed the durability of clinical benefit of BV in patients with relapsed or refractory systemic ALCL.[124] After a median follow-up of approximately 6 years, the ORR of 86% (66% CR and 21% PR) was similar to the previously reported ORR of 86% (59% CR) evaluated by an independent review committee. The estimated 5-year OS and PFS rates were 60% and 39%, respectively. The 5-year OS rate was higher for patients who achieved a CR (79% compared to 25% for those who did not achieve a CR). The median duration of objective response for all patients was 26 months (the median duration of response was not reached for patients with a CR). The ORRs were similar for patients with ALK-negative ALCL (88%; 52% CR) and those with ALK-positive ALCL (81%; 69% CR). The estimated 5-year OS and PFS rates were 61% and 39%, respectively, for patients with ALK-negative ALCL. The corresponding survival rates were 56% and 37%, respectively, for those with ALK-positive ALCL. Among patients who achieved a CR, the 5-year PFS rate was 60% for patients with ALK-negative ALCL and 50% for those with ALK-positive ALCL. Peripheral neuropathy was the most common adverse event reported in 57% of patients, with resolution or improvement reported in the majority of patients with long-term follow-up.[124] In August 2011, based on the results from this study, BV was approved by the FDA for the treatment of patients with systemic ALCL after failure of at least one prior multiagent chemotherapy regimen.

The planned subset analysis of a phase II multicenter study that evaluated the efficacy and safety of BV in relapsed/refractory CD30-positive NHL showed that it was also effective in other subtypes of relapsed PTCL, particularly AITL.[125] 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 patients with T-cell lymphoma were 41%, 8 months, and 3 months, respectively. The ORR (54% vs. 33%) and the median PFS (7 vs. 2 months) were better for patients with AITL than those with PTCL-NOS.

A retrospective study from the LYSA confirmed the efficacy of BV in combination with bendamustine in patients with relapsed/refractory PTCL (n = 82), particularly as a bridge to allogeneic HCT. The ORR was 68% (49% CR).[126] After a median follow-up of 22 months, the median PFS and OS were 8 months and 26 months respectively. The outcomes were better for patients who underwent allogeneic HCT after achieving CR. The median PFS was 19 months and the median OS was not reached.

Duvelisib

Preliminary findings from a dose optimization study confirmed that duvelisib (phosphatidylinositol 3-kinase [PI3K]-γ/δ inhibitor) monotherapy at 25 or 75 mg BID has clinical activity in patients with relapsed/refractory PTCL.[127] Early progression was seen more frequently in the 25 mg cohort, suggesting that higher initial doses may be required to achieve a more rapid tumor response. In the multicenter phase II trial (PRIMO), duvelisib was given at 75 mg twice daily for two cycles followed by 25 mg twice daily to maintain long-term disease control for patients with relapsed/refractory PTCL.[128] An interim analysis of dose-expansion cohort (78 patients) reported an ORR of 50% (32% CR). This activity was similar to the previously reported ORR of 50% (N = 8/16) in patients with PTCL from the phase I study.[129] Response rates were consistent across the most common subtypes including PTCL-NOS and AITL. Neutropenia (22%), infections (12%), elevated alanine transaminase (ALT) (24%) or aspartate aminotransferase (AST) (22%), diarrhea (3%), rash (8%), decreased lymphocyte count (8%), and sepsis (6%) were the most frequent grade ≥3 adverse events. This trial is ongoing with a targeted enrollment of 125 patients. The Panel consensus supported the inclusion

of duvelisib (75 mg BID for 2 cycles followed by 25 mg BID until disease progression) as an option for patients with relapsed/refractory PTCL.

Pralatrexate

In the pivotal, international phase II study (PROPEL) of heavily pretreated patients with relapsed or refractory PTCL (n = 109; 59 patients with PTCL-NOS; 13 patients with AITL, and 17 patients with ALCL), pralatrexate resulted in an ORR of 29% (CR 11%; response assessed by an independent central review). While the study was not statistically designed to analyze the ORR in specific subsets, response analyses by key subsets indicated that the ORR was lower in AITL (8%) than in the other two subtypes (32% and 35%, respectively, for PTCL-NOS and ALCL).[130] The median duration of response was 10 months. For all patients, the median PFS and OS were 4 months and 15 months, respectively. The most common grade 3–4 adverse events included thrombocytopenia (32%), neutropenia (22%), anemia (18%), and mucositis (22%).

The result of a pooled analysis from prospective clinical trials of single agent pralatrexate (n = 221; 48% patients with PTCL-NOS; 21% of patients with AITL and 12% of patients with ALCL, ALK-negative) also support the use of pralatrexate for patients with relapsed/refractory PTCL (ORR was 41%; the median PFS and OS were 5 months and 16 months, respectively).[131]

ALK Inhibitors

Crizotinib is FDA-approved for relapsed or refractory ALCL, ALK-positive in pediatric patients and young adults. Crizotinib also has demonstrated activity in adult patients with relapsed/refractory ALCL, ALK-positive after at least one line of prior cytotoxic therapy.[132] In a phase II study of 12 patients (median age at enrollment was 31 years; range 18–83 years), crizotinib (250 mg BID) resulted in an ORR of 83% (58% CR). The estimated 2-year PFS and OS rates were 65% and 66%, respectively.

Second-generation ALK inhibitors (alectinib, brigatinib, ceritinib) and third- generation ALK inhibitor (lorlatinib) also have demonstrated activity in relapsed or refractory ALCL, ALK-positive in single arm non-randomized studies.[133-138]

In an open-label phase II trial of 10 patients (aged ≥6 years; median age 19.5 years), alectinib (300 mg BID; patients weighing less than 35 kg were given a reduced dose of 150 mg BID), resulted in an ORR of 80% with estimated 1-year PFS and OS rates of 58% and 70%, respectively.[135] Alectinib was approved in Japan for relapsed/refractory ALCL, ALK-positive based on this study).

Brigatinib has shown efficacy in patients with relapsed/refractory ALCL, ALK-positive after prior therapy with BV and crizotinib.[136] In a study of 15 patients with previously treated ALCL, ALK-positive brigatinib resulted in an ORR of 93% (73% CR). After a median follow-up of 15 months, the 1-year PFS and OS rates were 72% and 85%, respectively.

Ceritinib also resulted in high ORR and longer duration of remission in a small number of patients (n = 3) with relapsed/refractory ALCL, ALK-positive included as part of a larger trial evaluating ceritinib in advanced or metastatic ALK-positive tumors.[137] Lorlatinib has demonstrated activity resulting in high response rates in patients with ALCL, ALK-positive previously treated with at least one ALK-inhibitor.[138]

Crizotinib does not have central nervous system (CNS) penetration. Alectinib, brigatinib, ceritinib, and lorlatinib have CNS penetration and could be considered as alternative options for patients with CNS involvement.[133,134]

Histone Deacetylase Inhibitors

HDAC inhibitors (eg, romidepsin, belinostat) have shown single-agent activity in patients with relapsed or refractory PTCL.[139-141]

Romidepsin received accelerated FDA approval in June 2011 for the treatment of relapsed/refractory PTCL based on the results of the pivotal multicenter phase II study that evaluated the impact of romidepsin on the surrogate endpoint of ORR (130 patients with relapsed/refractory PTCL; PTCL-NOS, n = 69 [53%]; AITL, n = 27 [21%]; ALCL, ALK-negative, n = 21 [16%]).[139] Updated results from this study confirmed that responses were durable across all three subtypes of PTCL.[140] At a median follow-up of 22 months, there were no significant differences in ORR or rates of CR between the three most common subtypes of PTCL. The ORRs were 29%, 30%, and 24%, respectively, for patients with PTCL-NOS, AITL, and ALCL, ALK-negative. The corresponding CR rates 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 for ≥12 months compared to those who achieved CR for <12 months or PR (29 months, 13 months, and 7 months, respectively). The median OS was not reached for patients who achieved CR and 18 months for those who achieved PR.[140] The most common grade ≥3 adverse events included thrombocytopenia (24%), neutropenia (20%), and infections (19%).[139]

In August 2021, the accelerated approval status for romidepsin for the treatment of relapsed/refractory PTCL was withdrawn following the results of the confirmatory phase III trial, which failed to meet the primary endpoint of improved PFS for romidepsin + CHOP in patients with previously untreated PTCL (421 patients randomized to receive romidepsin + CHOP or CHOP).[66] After a median follow-up of 28 months the addition of romidepsin to CHOP did not result in any statistically significant improvement in ORR, PFS, or OS but increased the frequency of grade ≥3 adverse events and the final analysis after a median follow-up of 6 years also confirmed these findings.[66,67] While the Panel acknowledged the change in the regulatory status of romidepsin, the consensus of the Panel was to continue the listing of romidepsin as an important option for relapsed or refractory PTCL based on the results of the earlier phase II study and subsequent studies in which romidepsin resulted in durable responses across all three subtypes of PTCL (ALCL, ALK-negative, PTCL-NOS, and AITL).[14,140]

The BELIEF trial evaluated belinostat in 129 patients with relapsed or refractory PTCL (pretreated with more than one prior systemic therapy).[141] The ORR in 120 evaluable patients was 26% (CR rate of 11% and PR rate of 15%). The median duration of response, median PFS, and median OS were 14 months, 2 months, and 8 months, respectively. The 1-year PFS rate was 19%.[141] The ORR was higher for AITL compared to other subtypes (45% compared to 23% and 15%, respectively, for patients with PTCL-NOS and ALCL, ALK-negative). Anemia (11%), thrombocytopenia (7%), dyspnea (6%), and neutropenia (6%) were the most common grade 3 or 4 adverse events. Belinostat was approved by the FDA in July 2014 for the treatment of relapsed or refractory PTCL. Belinostat induced responses across all types of PTCL (with the exception of ALCL, ALK-positive) and response rates were significantly higher for AITL than other subtypes.[141]

Ruxolitinib

A phase II biomarker driven study demonstrated the efficacy of ruxolitinib in patients with relapsed/refractory PTCL. In this study (n = 53; 45 patients with relapsed/refractory PTCL), patients were enrolled into 1 of 3 cohorts: presence of activating *JAK* and/or *STAT* mutations (cohort 1); ≥30% pSTAT3 expression by IHC (cohort 2) and cohort 3 had patients with neither of these criteria.[142] Clinical benefit rate (CBR; defined as the combination of CR, PR, and stable disease for at least 6 months) was the primary endpoint. In the subset of patients with PTCL, the CBR was 53%, 45%, and 13% for cohorts 1, 2, and 3, respectively (cohorts 1 and 2 vs. cohort 3; $P = .02$). The corresponding ORR were 37% (5% CR) 36% (18% CR) and 7% (all CRs).

Azacitidine

The efficacy of 5-azacitidine in patients with relapsed/refractory AITL or nodal TFH cell lymphomas was demonstrated in a phase III randomized study (86 patients randomized to receive oral azacitidine or single agent of investigator's choice [gemcitabine, bendamustine or romidepsin]), although the trial did not meet the primary end point for significant improvement in PFS.[143] After a follow-up of 14 months, the median PFS was 6 months for the azacitidine arm versus 3 months in the control arm. However, it did not reach the study required statistical level of significance of $P < .025$ ($P = .0421$). The median OS was 18 months and 10 months for the two arms, respectively.

Other Single Agents

Data to support the use of monotherapy with other single agents (alemtuzumab, bortezomib, cyclosporine, gemcitabine, and lenalidomide) are mainly from small single-institution series as described below.

Alemtuzumab and gemcitabine have demonstrated activity resulting in an ORR of 50% to 55% (CR, 30%–33%) in the subset of patients with PTCL-NOS.[144-146] Reduced-dose alemtuzumab was less toxic, equally effective, and was also associated with lower incidences of cytomegalovirus (CMV) reactivation compared to standard-dose alemtuzumab.[145]

Cyclosporine has been effective in patients with relapsed AITL following treatment with steroid or multiagent chemotherapy or HDT/ASCR.[147,148] Lenalidomide monotherapy has also been effective in the treatment of relapsed or refractory PTCL resulting in an ORR of 24% and it has been particularly active in patients with relapsed or refractory AITL resulting in an ORR of 31% (15% CR).[149,150]

Bortezomib has shown activity in relapsed/refractory PTCL-NOS and AITL (mostly in case reports).[151-153] In a single institution study of 12 patients (10 patients with mycosis fungoides and 2 patients with PTCL-NOS with isolated skin involvement), bortezomib resulted in an ORR of 67% (17% CR).

Combination Chemotherapy

There are very limited data available for the specific use of combination chemotherapy regimens in patients with relapsed or refractory PTCL (as discussed below).[154-157]

Aggressive second-line chemotherapy with ICE (ifosfamide, carboplatin, and etoposide) followed by autologous HCT was evaluated in patients with relapsed/refractory PTCL.[154] Among 40 patients treated with ICE, 27 (68%) underwent autologous HCT. 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 a significantly higher 3-year PFS rate compared to those with primary refractory (20% vs. 6%; $P = .0005$).

Gemcitabine, dexamethasone, and cisplatin (GDP) followed by autologous HCT has also been shown to be effective for the treatment of patients with relapsed or refractory PTCL, resulting in an ORR of 72% to 80% (CR, 47%–48%).[155,156] 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 ($P = .23$). The median PFS and OS after treatment with GDP were 4 months and 7 months, respectively for patients who did not receive transplant.[155]

The results of a retrospective analysis showed that the gemcitabine, vinorelbine, and doxorubicin (GND) regimen 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% and a median OS of 36 months. The 5-year estimated OS rate was 32%.[157]

The inclusion of other combination chemotherapy regimens for the treatment of relapsed/refractory PTCL are derived from aggressive lymphoma clinical trials that have also included a limited number of patients with PTCL.

Selection of Second-line Systemic Therapy

There are not enough data to support the use of a particular regimen for second-line therapy based on the subtype, with the exception of ALCL. BV should be the preferred choice for second-line therapy for relapsed/refractory ALCL.[123-125]

HDAC inhibitors or azacitidine may have superior activity in nodal TFH cell lymphomas compared to other subtypes.[14,15,141,143] In the BELIEF trial, response rates with belinostat were significantly higher for AITL than other subtypes.[141] Bendamustine and lenalidomide have also induced higher response rates in patients with AITL compared to those with other subtypes.[122,149] Cyclosporine may be appropriate for patients with relapsed AITL following treatment with steroids or multiagent chemotherapy or autologous HCT.[147,148] However, the aforementioned studies were not sufficiently powered to evaluate the response rates in specific subtypes. Pralatrexate has very limited activity in AITL compared to other subtypes.[130]

ALK inhibitors could be considered for ALCL, ALK-positive. Alectinib, brigatinib, ceritinib, and lorlatinib could be appropriate options for patients with CNS involvement.[134] Ruxolitinib has activity across all PTCL subtypes and the presence of activating *JAK/STAT* mutations or pSTAT3 expression by IHC (≥30%) resulted in higher CBR.[142]

The selection of second-line therapy 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 autologous HCT is being considered. Combination chemotherapy may also be preferred for patients who are ready to proceed to allogeneic HCT 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.

Results from the COMPLETE registry showed that treatment with single agents were often as effective, with a trend towards increased CR rate as combination regimens (41% vs. 19%; $P = .02$).[158] The median OS (39 vs. 17 months; $P = .02$) and PFS (11 vs. 7 months; $P = .02$) were also higher among patients treated with single agents, and more patients receiving single agents received HCT (26% vs 8%, $P = .07$). Similarly, in a meta-analysis of 151 studies that evaluated the outcomes of 6209 patients with relapsed or refractory T-cell lymphomas treated with either novel single agents, combination chemotherapy, combination of novel agents and combination chemotherapy, or the combination of novel agents, the response rates were not statistically different between the treatment approaches for the subset of patients with relapsed/refractory PTCL.[159] The ORR was 36% for single agents, 48% for combination chemotherapy 54% for single novel agents plus combination chemotherapy, and 45% for novel agent combinations. This observation remained unchanged when the analysis was restricted to either PTCL-NOS or AITL respectively.

Thus, for many patients with an intent to proceed to allogeneic HCT, single agents or combination regimens may be appropriately used as a bridge to transplant. Single agents or lower toxicity regimens may also be more appropriate for older patients with a limited performance status or for those

patients who are unable to tolerate more intensive combination chemotherapy. However, the preferential use of single agents versus combination regimens in patients with an intention to proceed to transplant has not been evaluated in a prospective randomized trial.

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Breast Implant-Associated ALCL

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is an uncommon and emerging peripheral T-cell lymphoma (PTCL), first reported in 1997.[1] BIA-ALCL represents a distinct entity from systemic ALCL and other forms of primary breast lymphoma (which are usually of B-cell origin).[2-11] The majority of cases have been reported in patients with a textured surface implant without any documented cases in patients receiving only a smooth surface implant.[10-17] The risk of BIA-ALCL following textured implants has ranged from 1 in 1000 to 1 in 50,000 based upon varied risk estimates due to differences in manufacturer texture on implants.[10,15,18] In a prospective cohort study of 3546 patients who underwent breast reconstructions with macro-textured implants (mainly after breast cancer resection, or contralateral prophylactic mastectomy), the overall risk of BIA-ALCL was 1 in 355 patients with "salt-loss type" *Biocell* texture (or 0.311 cases per 1000 person-years), which is higher than previously reported.[14]

In 2011, the U.S. Food and Drug Administration (FDA released a safety communication on an association between breast implants and ALCL, indicating that patients with breast implants may develop BIA-ALCL in an effusion or scar tissue adjacent to an implant. In 2019, the FDA issued a Class I device recall of Allergan *Biocell* textured implants and tissue expanders, and mandated the placement of a black box warning on all breast implants regarding the increased risk of lymphoma. In 2012, the FDA, the American Society of Plastic Surgeons (ASPS), and the Plastic Surgery Foundation (PSF) formed a prospective patient registry, entitled "Patient Registry and Outcomes for Breast Implants and ALCL Etiology and Epidemiology (PROFILE)," to prospectively track patients with BIA-ALCL.

BIA-ALCL is included as a distinct entity in the updated 2022 WHO classification (WHO5) and International Consensus Classification (ICC).[19,20] According to the updated information issued by the FDA on June 30, 2023, a total of 1264 cases of BIA-ALCL have been diagnosed and 63 deaths have been reported worldwide, which includes 330 confirmed cases in the United States reported to the PROFILE registry.[21,22] The prevalence of BIA-ALCL in the United States ranges from 1:300 to 1:50,000 with incidence rates of 4.5 per 10,000.[23] The frequency of BIA-ALCL remains underreported (limited mainly to the cases identified in the United States, Europe, and Australia) and the exact number of cases remains difficult to determine since the disease is emerging and federal reporting of BIA-ALCL has several limitations.[24] Prophylactic explantation of textured implants is not routinely recommended. However, following risk stratification, it may be deemed reasonable for risk reduction in select patients following an informed discussion regarding the benefits and risks of surgery.[25-27]

Literature Search Criteria

Prior to the update of this version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for T-Cell Lymphomas, a literature search of the PubMed database was performed to obtain key literature in BIA-ALCL since the previous Guidelines update. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[28]

The search results were narrowed by selecting studies in humans published in English. The data from key PubMed articles 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.

Clinical Presentation and Prognosis

Patients with BIA-ALCL present with physical signs (periprosthetic effusion, breast enlargement, tumor mass, rash, lymphadenopathy, and skin ulceration) more than 1 year after receiving a textured surface breast implant (mean time of presentation is 8–10 years post-implantation). Delayed seromas without systemic symptoms are the most common presentation of BIA-ALCL.[17] BIA-ALCL may be diagnosed at an earlier stage in patients with prior history of breast reconstruction due to breast cancer compared to those with cosmetic breast implants.[29]

BIA-ALCL may present along a spectrum of stages associated with different outcomes: in situ BIA-ALCL characterized by effusion around the implant and anaplastic cell proliferation confined to the fibrous scar capsule; infiltrative BIA-ALCL with pleomorphic cells aggregating into a mass progressing with adjacent tissue infiltration and chest wall invasion; regional lymph node involvement; and, rarely, organ and bone metastasis.[6,30] The effusion-limited variant (presenting in an effusion or confined by the fibrous capsule) generally has an indolent disease course and can be adequately treated with surgery alone with an excellent long-term survival. Infiltrative BIA-ALCL can have a more aggressive clinical course, and can still be amendable to surgical treatment if complete surgical excision is possible; however, it may require additional treatment following removal of the implant.[30] In a retrospective study that reported the long-term follow-up of 60 patients with BIA-ALCL, the complete remission rate was 93% for patients with disease confined to the fibrous capsule compared to 72% for those presenting with a tumor mass.[6] Clinical presentation with a breast mass was also associated with worse overall survival (OS; $P = .052$) and progression-free survival (PFS; $P = .03$). In another retrospective analysis of 19 patients with BIA-ALCL, after 18 months of median follow-up, the 2-year OS rates were 100% and 53%, respectively, for in situ and infiltrative BIA-ALCL.[30]

BIA-ALCL is associated with a good prognosis with the majority of patients presenting with localized disease (periprosthetic effusion with no tumor mass), whereas systemic involvement has also been less commonly reported (tumor mass with or without effusion or lymph node involvement).[6,18,30-33] Unresectable disease and lymph node metastasis have higher rates of relapse.[30,31,33,34] The event-free survival (EFS) and OS rates were better for patients with resectable BIA-ALCL confined to the fibrous capsule surrounding the implant compared to patients with invasive BIA-ALCL that had spread beyond the capsule.[31] Parenchymal breast or lymph node involvement, although less common, may have an aggressive clinical course more in line with systemic anaplastic lymphoma kinase (ALK)-positive ALCL. A study that assessed the clinical and histopathologic features of lymph nodes in 70 patients with BIA-ALCL reported lymph node involvement in 20% of patients (regional axillary lymph node involvement was the most frequently observed location in 93% of patients followed by clavicular and internal mammary lymph node basins).[33] BIA-ALCL beyond the capsule was associated with higher risk of lymph node involvement (38% compared to 12% in patients with tumor confined by the capsule). The 5-year OS rates were 75% and 98%, respectively, for patients with and without lymph node involvement at presentation.

Diagnosis and Pathologic Workup

Initial workup should include ultrasound (US) of breast and axilla or breast MRI in selected cases or PET/CT scan in selected cases. In patients with BIA-ALCL, the sensitivity of US for detecting an effusion (84%) or a mass (46%) was similar to that of MRI (82% and 50%, respectively).[7] Patients with suspected BIA-ALCL should be first evaluated with US, regardless of age or implant type.[35] If US is inconclusive, breast MRI should be performed if not done previously.

Cytologic evaluation and biopsy (fine-needle aspiration [FNA] biopsy of periprosthetic effusion and/or biopsy of the tumor mass) with adequate immunophenotyping (immunohistochemistry [IHC] and flow cytometry) are essential for an accurate diagnosis of BIA-ALCL.[36-38] Biopsy (excisional or incisional or core needle) may be required for diagnosis, if there is solid mass associated with the implant. Multiple systematic scar capsule biopsies may be necessary to determine early invasive disease and mass formation, which have implications for prognosis.[39]

Biopsy specimens show large pleomorphic tumor cells of T-cell lineage with a strong and uniform expression of CD30 with variable CD3-, CD5-, CD4+, and CD43+.[5,6,40] IHC and flow cytometry should include CD2, CD3, CD4, CD5, CD7, CD8, CD30, CD45, and ALK. CD30 enzyme-linked immunosorbent assay (ELISA) might be a viable screening tool for BIA-ALCL.[41] Flow cytometry immunophenotyping can be used as an adjunct to IHC.[42] However, confirmation of diagnosis requires pathology evaluation with CD30 IHC and the use of flow cytometry alone as the sole diagnostic method is not recommended to confirm the diagnosis of BIA-ALCL.

Cases of BIA-ALCL reported to date have all been negative for *ALK, DUSP22*, and *TP63*, which have been associated with systemic ALCL.[43] Recurrent mutations associated with the constitutive activation of JAK-STAT3 pathway, *TP53* mutations, as well as mutations of epigenetic modifiers (eg, *DNMT3A*) have been identified in some cases.[43-50] *TP53* mutation is associated with high-risk disease in a variety hematologic malignancies and BIA-ALCL with *TP53* mutation appears to have a more invasive disease with mass, faster disease progression, and more lymph node metastasis.[25,51] Therefore, next-generation sequencing (NGS) to identify the presence of high-risk mutations may have prognostic value at time of diagnosis.[44]

Referral to a plastic surgeon for appropriate management of an implant seroma is recommended if the pathologic diagnosis is negative for BIA-ALCL. A second pathology consultation in a tertiary cancer center is recommended if the pathologic diagnosis is indeterminate for BIA-ALCL. Histologically confirmed BIA-ALCL requires individualized management by a multidisciplinary team including a medical oncologist, surgical oncologist, plastic surgeon, and hematopathologist. In accordance with the FDA recommendation, all cases of histologically confirmed BIA-ALCL should be reported to the BIA-ALCL PROFILE Registry (http://www.thepsf.org).

Lymphoma Workup and Staging

The workup should include history and physical examination, routine laboratory studies (ie, complete blood count [CBC] with differential, comprehensive metabolic panel, serum lactate dehydrogenase [LDH]), and PET/CT scan. Multigated acquisition (MUGA) scan or echocardiogram is also recommended, if anthracycline- or anthracenedione-based chemotherapy is indicated. Bone marrow biopsy is only needed in selected patients with extensive disease or unexplained cytopenia.

A unique tumor node metastasis (TNM) staging system is used to better stratify and predict prognosis given that the Lugano modification of the Ann Arbor staging system does not help to risk stratify patients with BIA-ALCL.[31] This staging system divided patients with BIA-ALCL into a spectrum of multiple prognostic groups: stage IA (36%); stage IB (12%); stage IC (14%); stage IIA (25%); stage IIB (5%); stage III (9%); and stage IV (0%). The EFS was significantly higher for patients with stage I disease than for those with higher stage disease (P = .003), and the rate of events was 3-fold higher for stage II or III compared with stage I disease.

Treatment

Total capsulectomy with removal of the breast implant and excision of any associated mass with a biopsy of suspicious lymph nodes is

recommended for all patients.[6,31,52] Immediate (early-stage) or delayed (advanced-stage) breast reconstruction with autologous tissue or smooth surface breast implants may be considered.[53] Removal of the contralateral implant can be considered since simultaneous or subsequent bilateral breast involvement has been reported in approximately 5% of patients with BIA-ALCL.[31,54] As BIA-ALCL is not a disease of the breast parenchyma, there is no role for mastectomy or sentinel lymph node biopsy.

Consultation with a surgical oncologist is recommended for patients with a preoperative mass since complete surgical excision alone is the optimal treatment for patients with localized disease (stage IA–IC) who present with effusion (with or without a distinct breast mass). In a retrospective study of 87 patients with BIA-ALCL (52 patients presented with effusion only; 15 patients presented with a mass only, and 17 patients had effusion and mass), the OS rates (P = .022) and EFS rates (P = .014) were significantly better for patients who underwent complete surgical excision (total capsulectomy with breast implant removal and complete removal of any disease or mass with negative margins) compared to those who received partial capsulectomy, systemic chemotherapy, or radiation therapy (RT).[31] The 3-year OS and EFS rates were 94% and 49%, respectively, for the entire study group. The 5-year OS and EFS rates were 91% and 49%, respectively.

Observation (history and physical examination every 3–6 months for 2 years and then as clinically indicated] with or without contrast-enhanced CT or PET/CT [not more often than every 6 months for 2 years and then only as clinically indicated]) is recommended for all patients with localized disease following complete surgical excision with no residual disease.

Adjuvant treatment may be required for patients who undergo incomplete surgical excision or partial capsulectomy with residual disease (with or without regional lymph node involvement). However, there are very limited data to recommend an optimal approach and adjuvant treatment options should be discussed with a multidisciplinary team.[55] RT for local residual disease ± systemic therapy may be beneficial, following incomplete excision or partial capsulectomy.[6,31] Systemic therapy (if RT is not feasible) could be considered for patients with lymph node involvement. Advanced-stage disease is associated with higher rates of limited surgery, compared to those with early-stage disease.[56] Systemic therapy should be considered for patients presenting with an unresectable mass or those with extended disease (stage II–IV). High-dose therapy followed by autologous hematopoietic cell transplant (HCT) could be considered for patients achieving complete response to systemic therapy.

Due to the rarity of advanced BIA-ALCL, the data for the use of systemic therapy is extrapolated from clinical studies that have evaluated treatment options for systemic ALCL. Chemotherapy regimens recommended for systemic ALCL have been used in some patients with BIA-ALCL, although the use of chemotherapy was not associated with better OS or PFS (P = .44 and P = .28, respectively).[6,31,57] Brentuximab vedotin (BV) has also shown promising clinical activity in anecdotal reports.[58,59] In the phase III randomized trial (ECHELON-2), brentuximab vedotin (BV) in combination with CHP (cyclophosphamide, doxorubicin, and prednisone) resulted in significantly improved PFS and OS compared to CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) in patients with previously untreated CD30-positive PTCL and the survival benefit was clearly established for the subset of patients with ALCL.[60] BV in combination with CHP is FDA-approved as first-line therapy for patients with untreated systemic ALCL. BV (monotherapy or in combination with CHP) is included as a preferred systemic therapy option for BIA-ALCL. CHOP, CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone), or dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) are included as alternative options (other recommended regimens).

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T-Cell Large Granular Lymphocytic Leukemia

Large granular lymphocytic leukemia (LGLL) is a rare chronic lymphoproliferative disorder originating in the mature T cells and natural killer (NK) cells, accounting for 2% to 5% of all the chronic lymphoproliferative disorders in North America and Europe. In the 2017 WHO classification, LGLL was classified into three categories: T-cell LGLL (T-LGLL), chronic lymphoproliferative disorder of NK cells (included as a provisional entity), and aggressive NK-cell leukemia (ANKL).[1] In the updated 2022 WHO classification (WHO5), chronic lymphoproliferative disorder of NK cells is renamed as NK-LGLL and is listed as a definite entity.[2] The 2022 International Consensus Classification (ICC) continues to list chronic lymphoproliferative disorder of NK cells as a provisional entity.[3]

T-LGLL is the most common subtype, representing approximately 85% of LGLL cases, and NK-LGLL represents approximately 10% of LGLL cases.[4-6] Most of T-LGLL are of αβ T-cell origin, but some also have γδ T-cell phenotype. NK-LGLL has clinical and biologic features similar to T-LGLL and is managed similar to T-LGLL.[7-9] ANKL, mainly diagnosed in Asia, represents approximately 5% of LGLL cases. It is associated with Epstein-Barr virus (EBV) infection and the prognosis is very poor since it is refractory to chemotherapy.[10]

Literature Search Criteria

Prior to the update of this version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for T-Cell Lymphomas, a literature search of the PubMed database was performed to obtain key literature in T-LGLL since the previous Guidelines update. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes 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 data from key PubMed articles 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.

Diagnosis

The diagnosis of LGLL requires the presence of an expanded clonal population of T- or NK-cell large granular lymphocytes. Large granular lymphocyte count of greater than 500 x 10^9/L is typically needed, but not required for the diagnosis of T-LGLL, although patients with concomitant bone marrow failure/pancytopenia may not meet this threshold. Therefore, the diagnosis of T-LGLL should be based on clinicopathologic findings, especially in those patients with large granular lymphocyte count less than 500 x 10^9/L in the peripheral blood.

Morphologic examinations of peripheral blood smear, as well as flow cytometry with adequate immunophenotyping, are essential to confirm the diagnosis of T-LGLL. Bone marrow aspirate and biopsy is not essential for initial evaluation. However, bone marrow biopsy with immunophenotyping is useful for patients with low large granular lymphocyte count (<0.5 x 10^9/L) and is also useful when considering the differential diagnosis of concurrent bone marrow failure disorders.[12-14]

Typical immunophenotype for T-LGLL is consistent with that of mature post-thymic phenotype in the vast majority of cases. T-LGLL is CD3+, CD8+, CD16+, CD57+, CD56-, CD28-, CD5 dim and/or CD7 dim, CD45RA+, CD62L-, TCRαβ+, TIA1+ and granzyme B+, and granzyme

M+.[12-14] Typical immunophenotype for NK-LGLL is CD3−, CD8+, CD16+, CD56+, CD4−, CD94+, and TCRαβ−.[5]

Flow cytometry should include the following markers: CD3, CD4, CD5, CD7, CD8, CD16, CD56, CD57, CD28, TCRαß, TCRγδ, CD45RA, and CD62L. The immunohistochemistry (IHC) panel should include CD3, CD4, CD5, CD7, CD8, CD56, CD57, TCRß, TCRγ, TIA1, perforin, and granzyme B. Granzyme M is expressed in LGLL of both T-cell and NK-cell lineage, and IHC for granzyme M may be useful in selected circumstances.[15]

Assessment of T-cell clonality either by molecular analysis for the detection of clonal *TCR* gene rearrangements or other assessment of clonality is useful under selected circumstances.[16-20] However, *TCR* gene rearrangement results should be interpreted with caution, since *TCR* gene rearrangement without cytologic and immunophenotypic evidence of abnormal T-cell population can also be seen in healthy patients. Small, clinically non-significant clones of large granular lymphocytes can be detected concurrently in patients with bone marrow failure disorders. Therefore, it is essential to rule out reactive large granular lymphocytic lymphocytosis in patients with autoimmune or bone marrow failure disorders. Flow cytometry and *TCR* gene rearrangement studies should be repeated in 6 months in asymptomatic patients with small clonal large granular lymphocytes (<0.5 x 10^9/L) or polyclonal large granular lymphocytic lymphocytosis.

Somatic mutations in the *STAT3* and *STAT5B* genes have been identified in patients with LGLL.[21] *STAT3* mutations are more common in patients with T-LGLL and NK-LGLL.[22-28] *STAT5B* mutations have been identified in a smaller proportion of patients and are more common in patients with CD4+ T-LGLL.[29,30] Recent reports have identified specific molecular subtypes of T-LGLL based on the *STAT3* or *STAT5B* mutation status (CD8+ T-LGLL with CD16+/CD56- immunophenotype was characterized by the presence of *STAT3* mutations and neutropenia whereas T-LGLL with CD4+/CD8 +/- immunophenotype are devoid of *STAT3* mutations but characterized by *STAT5B* mutations), and *STAT3* mutations have also been associated with reduced overall survival (OS) and shortened time to treatment.[31-33]

Mutational analysis for *STAT3* and *STAT5B* is useful under certain selected circumstances. Epstein-Barr encoding region (EBER) in situ hybridization is useful under certain selected circumstances for the differential diagnosis of ANKL.[10]

Workup

The initial workup for T-LGLL should include comprehensive medical history and physical examination, including careful evaluation of lymph nodes, spleen, and liver, in addition to evaluation of performance status and the presence of autoimmune disorders. Laboratory assessments should include complete blood count (CBC) with differential, comprehensive metabolic panel, serology studies for the detection of antibodies against HIV (type 1 and type 2) and human T-cell lymphotropic virus (HTLV; type 1 and type 2), as well as polymerase chain reaction (PCR) for viral DNA or RNA.

Autoimmune disorders and immune-mediated cytopenias can occur in patients with T-LGLL.[34,35] Rheumatoid arthritis, often with concomitant Felty syndrome (splenomegaly, neutropenia, and rheumatoid arthritis) is the most common autoimmune disorder associated with T-LGLL, although other less common diseases such as Sjogren syndrome or other autoimmune disorders have also been described.[35-37] Pure red cell aplasia (PRCA) is one of the most common complications of LGLL in Asian patients.[38] Evaluation of serologic markers such as rheumatoid factor (RF), antinuclear antibodies (ANA), and erythrocyte sedimentation rate (ESR) is useful in patients with autoimmune disease.

Imaging studies, including ultrasound of liver/spleen and chest/abdomen/pelvis CT scan with contrast of diagnostic quality echocardiography (for patients with unexplained shortness of breath and/or right heart failure) may also be useful under selected circumstances.

Treatment Options

First-line Therapy

Because T-LGLL is relatively rare, few clinical trials have been conducted and treatment recommendations are based on evidence mainly from retrospective studies. Methotrexate, cyclophosphamide, and cyclosporine are used most commonly for first-line therapy.[39-54]

In the first prospective phase II trial of 59 patients with T-LGLL (ECOG5998), 55 eligible patients received first-line therapy with low-dose methotrexate (10 mg/m^2) and prednisone (1 mg/kg orally for 30 days and then tapered off in the subsequent 24 days) resulting in an overall response rate (ORR) of 38% (5% complete response [CR] and 33% partial response [PR]).[48] The ORRs were 42%, 34%, and 29%, respectively, for patients with neutropenia, anemia, and rheumatoid arthritis.

In a single-center series of 39 patients with T-LGLL (15 patients never required treatment), among the 24 patients requiring treatment, 9 patients received low-dose methotrexate as first-line therapy, resulting in an ORR of 89% and the median duration of response was 133 months.[49] Among 5 patients treated with methotrexate after disease progression on prednisolone, the ORR was 100% and the median duration of response was 14 months.

In another single-center cohort study of 204 patients with LGLL (90% had T-LGLL and 10% had NK-LGLL), cyclosporine, methotrexate, and cyclophosphamide were given as first-line therapy in 37%, 29%, and 19% of patients, respectively.[51] Initial response rates were 45%, 47%, and 44%, respectively, for cyclosporine, cyclophosphamide, and methotrexate. Many patients received multiple therapies due to lack of initial response and/or toxicity. The combined ORRs were 48%, 53%, and 43%, respectively. Methotrexate resulted in more durable responses (36 months) than cyclosporine (21 months) or cyclophosphamide (14 months). *STAT3* mutations were associated with significantly longer median OS. After a median follow-up of 36 months, the median survival was 118 months in patients without a *STAT3* mutation and the median survival was not reached in those with a *STAT3* mutation. However, in a more recent report *STAT3* mutation was independently associated with reduced OS.[32]

Another series of 23 patients with T-LGLL reported ORR and CR rates of 78% and 30%, respectively, with cyclosporine as first-line therapy.[41] In a series of 45 patients with LGLL, cyclophosphamide (with or without prednisone) as a first-line therapy resulted in an ORR of 71% (47% CR and 24% PR).[47] The ORR was 72% and 68%, respectively, for patients with T-LGLL and NK-LGLL, and 72% and 67%, respectively, for patients with neutropenia and anemia.

In another retrospective analysis of 60 patients with T-LGLL that evaluated the clinical outcomes using the stringent response criteria from the ECOG5998 study, the ORR to first-line methotrexate was 41% (10% CR) and the median duration of response was 17 months.[53] No patients treated with first-line cyclosporine or cyclophosphamide had a response. Among the 10 patients who received first-line methotrexate, cyclophosphamide resulted in an ORR of 70%, suggesting this is an effective second-line therapy option.

In a single center cohort study of 319 patients with LGLL (295 patients with T-LGLL), monotherapy with methotrexate, cyclophosphamide, or cyclosporine were most commonly used as first-line therapy.[54] The CR rates were higher with cyclophosphamide (32%) compared to methotrexate (16%) or cyclosporine (23%). The presence of autoimmune

diseases was associated with increased response rates, whereas thrombocytopenia, splenomegaly, and female gender assigned at birth (after controlling for autoimmune diseases) were associated with decreased response rates. Thrombocytopenia was also an independent risk factor for inferior survival.

An ongoing prospective clinical trial is comparing methotrexate with cyclophosphamide in patients with previously untreated LGLL in need of treatment, although early results suggest no clear difference.[55]

NCCN Recommendations

Treatment should be initiated in symptomatic patients in the presence of indications for treatment, which include: absolute neutrophil count (ANC) less than 0.5 x 10^9/L, ANC less than 1500 x 10^9/L with recurrent infections or hospitalizations for neutropenic fever, hemoglobin less than 10 g/dL, or the need for red blood cell (RBC) transfusion, platelet count less than 50 x 10^9/L, autoimmune diseases associated with T-LGLL requiring treatment, symptomatic splenomegaly, and pulmonary artery hypertension secondary to LGLL.

Low-dose methotrexate or cyclophosphamide (with or without corticosteroids) or cyclosporine are included as options for first-line therapy. Patients with active autoimmune disease should have therapy directed toward their autoimmune disease whenever possible, and low-dose methotrexate may be beneficial for patients with concomitant autoimmune disease. Cyclophosphamide or cyclosporine may be used in patients with anemia.

Response assessment should be done after 4 months of first-line therapy and the use of the parameters established in the ECOG5998 study are recommended for the assessment of response, including the use of peripheral blood flow cytometry. Continuation of initial treatment is recommended for patients achieving CR or PR after 4 months. Treatment with cyclophosphamide should be limited due to increased risk of bladder toxicity, mutagenesis, and leukemogenesis (4 months if there is no response and up to ≤12 months if PR is achieved at 4 months).[56]

Relapsed or Refractory Disease

Cyclophosphamide and cyclosporine are also effective for disease not responding to initial treatment with methotrexate.[48,57,58] In the ECOG5998 trial that evaluated methotrexate with prednisone as first-line therapy, cyclophosphamide resulted in an ORR of 64% in patients with T-LGLL that did not respond to methotrexate.[48] Alemtuzumab is also active in patients with relapsed and refractory disease, resulting in an ORR of 56%.[59] While alemtuzumab is no longer commercially available, it may be obtained for clinical use. Purine analogues, including pentostatin, cladribine, and fludarabine have shown activity in refractory T-LGLL (mostly in small series or case reports).[41,42,44,60-62] Splenectomy can be considered in select patients non-responsive to standard agents, with concomitant splenomegaly and refractory cytopenia, particularly with autoimmune hemolytic anemia.[63]

Ruxolitinib (JAK inhibitor) has been evaluated in patients with relapsed or refractory T-LGLL.[64-66] Given the encouraging initial responses with ruxolitinib reported in a phase II biomarker driven study (that initially included patients with other relapsed/refractory T-cell lymphoma subtypes), the study included an expansion cohort of patients with relapsed/refractory LGLL (n = 23; 54% of patients had *STAT3* mutations).[66] Among 20 patients evaluable for response, the ORR was 55% (30% PR and 25% CR). The median EFS was not reached and 21-month EFS rate was 68%. Anemia (70%; grade 3, 44%) and neutropenia (65%; grade 3, 33%) were the most common adverse events. *STAT3* mutation status was a predictor of improved EFS (*P* = .007).[66] The median EFS was not reached and the 21-month EFS rate was 100% for

patients with *STAT3* mutation. The median EFS was 20 months and the 21-month EFS rate was 40% for those with no *STAT3* mutation.

NCCN Recommendations

Alternate first-line therapy or alemtuzumab or ruxolitinib is recommended for patients with disease not responding to initial treatment. Clinical trial, ruxolitinib (if not previously given), and purine analogues are included as preferred options for second-line therapy for progressive disease or refractory disease to all regimens. Alemtuzumab (if not previously given) is an option under other recommended regimens.

Ruxolitinib was dosed at 20 mg BID in the aforementioned phase II study.[66] Due to the prevalence of cytopenias in patients with LGLL, ruxolitinib dose reductions to 10 or 5 mg BID can be considered. Frequent CBC monitoring is recommended. Routine monitoring for cytomegalovirus (CMV) reactivation and the use of anti-infective prophylaxis for herpes virus and *Pneumocystis jirovecii* pneumonia (PJP) is recommended for all patients receiving alemtuzumab-based regimens. See *Supportive Care: Monoclonal Antibody Therapy and Viral Reactivation* in the algorithm.

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T-Cell Prolymphocytic Leukemia

Overview

T-cell prolymphocytic leukemia (T-PLL) is a rare malignancy, comprising approximately 2% of all mature lymphoid malignancies.[1,2] Clinically, patients frequently present with B symptoms, lymphadenopathy, hepatomegaly, splenomegaly, and elevated white blood cell (WBC) counts.[3] Rarely, patients can present with an asymptomatic leukocytosis. Skin lesions can also be present in approximately 30% of patients, although the cutaneous presentation is not well characterized. Central nervous system (CNS) involvement is rare and is seen in less than 10% of patients.[4,5]

Literature Search Criteria

Prior to the update of this version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for T-Cell Lymphomas, a literature search of the PubMed database was performed to obtain key literature in T-PLL published since the previous Guidelines update. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes 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; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The data from key PubMed articles 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.

Diagnosis

The diagnosis of TPLL is established if all three major criteria (T-lymphocytosis, >5 x10^9/L cells of T-PLL phenotype in peripheral blood or bone marrow; T-cell clonality confirmed by polymerase chain reaction or by flow cytometry; abnormalities in chromosome 14 or overexpression of *TCL-1* or *MTCP-1* oncogene) or if the first two major criteria and any one of the minor criteria (abnormalities involving chromosome 8 or 11; abnormalities in chromosomes 5, 12, 13, 22, or complex karyotype or the presence of splenomegaly or effusions) are present.[3]

Morphologic examinations of peripheral blood smear, as well as adequate immunophenotyping by flow cytometry, are essential to establish the diagnosis of T-PLL.[3] In most cases (approximately 75%), the typical morphology comprises medium-sized prolymphocytes with agranular basophilic cytoplasm and a single visible nucleolus, while in approximately 20% to 25% of cases, the cell is small and the nucleolus may not be readily visible.[1,2] Diffuse infiltration in the bone marrow is typically observed with T-PLL, but diagnosis is difficult to establish based on bone marrow evaluation alone. In general, bone marrow biopsy is not essential for establishing a diagnosis of T-PLL.[3]

The immunophenotype of T-PLL is consistent with a mature post-thymic T-cell phenotype, with a typical immunophenotype that is TdT-, CD1a-, CD2+, CD5+, and CD7+. CD3 expression may be weak on the cell surface but is usually expressed in the cytoplasm. In 65% of cases, the cells are CD4+/CD8- but cases with CD4+/CD8+ (21%) and CD4-/CD8+ (13%) can also be seen.[7] CD52 is often highly expressed.[8] 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.[9-12] Abnormalities in chromosome 8, mainly trisomy 8q, are also frequently observed.[9,10]

Cytogenetics by conventional karyotyping and/or fluorescence in situ hybridization (FISH) to detect chromosome 14 abnormalities and trisomy 8 should be performed at the time of diagnostic workup. Molecular testing to detect clonal *TCR* gene rearrangements and immunohistochemistry (IHC) analysis on bone marrow biopsy samples may be useful under certain circumstances. In such cases, the IHC panel should include TdT, CD1a, CD2, CD3, CD5, and TCL-1. Peripheral blood flow cytometry analysis should include the following markers: TdT, CD1a, CD2, CD3, CD4, CD5, CD7, CD8, CD52, and TCRαβ. Detection of TCL-1 overexpression by flow cytometry or IHC is more sensitive than cytogenetics.[3]

Although less frequent, the translocation t(x;14)(q28;q11), leading to overexpression of the *MTCP-1* oncogene, may also occur.[13,14] 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.[15,16] *ATM* gene is mutated in patients with ataxia telangiectasia, and these patients appear to be predisposed to developing T-cell lymphomas, 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.[15,16] Next-generation sequencing (NGS) studies have identified a high frequency of mutations in genes in the *JAK-STAT* pathway that could contribute to the pathogenesis of T-PLL,[17-20] and *JAK3* mutations have been associated with a significant negative impact on overall survival (OS).[21] The presence of complex karyotype (≥5 cytogenetic abnormalities) has also been reported as a poor prognostic factor in patients with T-PLL.[22]

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 complete blood count (CBC) with differential, a comprehensive metabolic panel, as well as measurements of serum lactate dehydrogenase (LDH). In a retrospective study of 119 patients with T-PLL, the presence of pleural effusion, elevated LDH, and low hemoglobin levels were associated with shorter OS.[23] 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.[3] 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 multigated acquisition (MUGA) scan or echocardiogram should be obtained for the evaluation of cardiac function, 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 enzyme-linked immunoassay (ELISA), a confirmatory Western blot should be performed. Screening for active infections and cytomegalovirus (CMV) serology should be strongly considered prior to initiation of treatment with alemtuzumab alone or in combination regimens. Human leukocyte antigen (HLA) typing is recommended for patients eligible for transplant.

Treatment Options

Systemic Therapy

Pentostatin (monotherapy or in combination with alemtuzumab) has shown activity in patients with TPLL.[7,23-26] In a study of 78 patients with T-PLL treated with alkylating agents, pentostatin, or CHOP, the median

OS was only 8 months; among the subgroup of patients with disease responding to pentostatin (n = 15), the median OS was 16 months.[7] In a retrospective analysis of patients with post-thymic T-cell malignancies treated with pentostatin, the overall response rate (ORR) was 45% (complete response [CR] rate of 9%) for patients with T-PLL (n = 55).[25] The median duration of response was short, however, at 6 months (range, 3-16 months). The median OS from treatment initiation was 18 months for responding disease and 9 months for non-responding disease.[25]

The anti-CD52 monoclonal antibody alemtuzumab (monotherapy or in combination regimens) has also been evaluated in patients with T-PLL.[23,26-31] In a retrospective analysis of 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).[23] The ORR and CR rates 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. 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).[26] The median progression-free survival (PFS) and OS for this subgroup of patients were 8 months and 10 months, respectively. The study included both patients with previously treated and untreated disease.

In a study that primarily included patients with pretreated T-PLL, intravenous (IV) alemtuzumab resulted in an ORR of 76% (60% CR rate).[28] 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 62% were resistant to prior treatments.[28] The median OS for all patients was 10 months, and was 16 months for patients with a CR. Following alemtuzumab, 11 patients underwent hematopoietic cell transplant (HCT) (autologous HCT, n = 7; allogeneic HCT, n = 4).

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 40%); among the 4 patients who received alemtuzumab as first-line therapy, 3 achieved a CR.[29] The time to progression (TTP) for all patients was 4.5 months, and the median OS was 7.5 months. Among the patients who achieved a CR, the median response duration and OS were 9 months and 15 months, respectively.[29] The most common toxicities reported with alemtuzumab in patients with T-PLL included infusion-related reactions, prolonged lymphocytopenia, and infectious events, including opportunistic infections.[28,29]

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, and mitoxantrone) followed by alemtuzumab maintenance in patients who were previously treated (n = 9) and treatment-naive (n = 16).[30,31] Patients with stable disease (SD) or progression after 2 courses of FCM were also eligible to receive alemtuzumab maintenance (21 patients subsequently received IV alemtuzumab maintenance following FCM chemotherapy). The ORR after FCM was 69% (31% CR and 38% partial response [PR]) and the ORR increased to 92% with a CR rate of 48% (intent-to-treat population) after alemtuzumab maintenance. 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 21 patients who received alemtuzumab maintenance, 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.

IV alemtuzumab is preferred over subcutaneous (SC) alemtuzumab based on data showing that the SC alemtuzumab is associated with inferior response rates and survival compared to IV alemtuzumab.[31-33] IV alemtuzumab results in high CR rates in patients with previously untreated T-PLL (ORR of 91%; 81% CR) as well as relapsed/refractory T-PLL (ORR of 74%; 60% CR) compared to SC alemtuzumab (33% CR).[32] In a retrospective analysis of 41 patients with T-PLL, there was a significant survival difference among patients treated with IV and SC alemtuzumab (41 vs.14 months; *P* = .0014).[33] The aforementioned prospective multicenter phase II study that evaluated induction chemotherapy with FCM followed by alemtuzumab maintenance also confirmed that IV alemtuzumab is preferred over SC alemtuzumab in patients with T-PLL.[31]

A biomarker driven study confirmed the efficacy of ruxolitinib (JAK inhibitor) in patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) subtypes.[34] In this study, a total of 53 patients were enrolled into one of the 3 cohorts: cohort 1 (presence of activating *JAK* and/or *STAT* mutations); cohort 2 (≥30% pSTAT3 expression by IHC); cohort 3 (if neither of the criteria for cohort 1 or 2 are present). The ORR were 33%, 29%, and 12%, respectively for patients in cohorts 1, 2, and 3. Among patients with TPLL (n=8; 7 patients with *JAK* and/or *STAT* mutations; 1 patient with ≥30% pSTAT3 expression by IHC), the ORR was 38% (3/8 patients) and all were transient partial responses.

Hematopoietic Cell Transplant

The potential utility of allogeneic HCT in patients with T-PLL has been reported in a number of individual case studies and retrospective analyses.[35-44]

In a review of data from the Center for International Blood and Marrow Transplant Research (CIBMTR) database (47 patients with T-PLL treated with allogeneic HCT), the 1-year PFS and OS rates were 33% and 48%, respectively.[39] 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 treatment-related mortality (TRM) and the incidence of relapse or disease progression were 28% and 39%, respectively.

In another retrospective study that evaluated the outcome of allogeneic HCT in 41 patients with T-PLL from the European Group for Blood and Marrow Transplantation (EBMT) database, the median PFS, median OS, and 3-year relapse-free survival (RFS) and OS rates were 10 months, 12 months, 19%, and 21%, respectively.[40] The 3-year TRM and relapse rates were 41% for both endpoints; most relapses (71% of cases) occurred within the first year following transplant. Patients who underwent HCT in first remission (CR or PR) tended to have a lower relapse rate (2-year rate: 30% vs. 46%) and higher event-free survival (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.

In a retrospective study that reported the outcomes of allogeneic HCT in 27 patients with T-PLL identified in the registry for French Society for stem cell transplantation, 21 patients achieved a CR as the best response following HCT (CR rate of 78% after HCT).[41] The majority of patients (85%) had received alemtuzumab prior to HCT (14 patients had a CR and 10 patients had a PR). 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%.

In an EBMT prospective observational study that assessed the outcome of allogeneic HCT in 37 evaluable patients with T-PLL (95% of patients had received prior alemtuzumab and 30% of patients received a conditioning regimen that included ≥6 Gy of TBI), the 4-year non-relapse mortality (NRM), PFS, and OS rates were 32%, 30%, and 42%, respectively.[44] At the time of transplant, the CR rate was 62%. The median follow-up was 50 months. In a univariate analysis, the use of TBI in the conditioning regimen was the only significant predictor for a low relapse risk, and an interval between diagnosis and allogeneic HCT of greater than 12 months was associated with a lower NRM.

Data from retrospective studies discussed above suggest that allogeneic HCT may offer the best chance for long-term disease control in a subgroup of patients with T-PLL, and a more recent retrospective analysis also reported that first-line therapy with alemtuzumab followed by consolidation with allogeneic HCT was associated with better outcomes.[45] However, allogeneic HCT is associated with higher rate of TRM. [39-41] Reduced-intensity conditioning prior to allogeneic HCT has been identified as a predictor of long-term disease-free survival in a multivariable analysis.[39-41,46]

Retrospective studies have also reported favorable survival outcomes with autologous HCT after alemtuzumab, and autologous HCT could be an alternative option for consolidation therapy.[47,48] In a retrospective study that reviewed the outcomes of 28 patients with T-PLL treated with either allogeneic (n = 13) or autologous HCT (n = 15) after alemtuzumab, no statistically significant difference in OS was observed between autologous versus allogeneic HCT (52 vs. 33 months).[47] Another retrospective analysis of 40 patients with T-PLL treated with autologous HCT reported an ORR of 88%. The 4-year OS and PFS rates were 34%, and 29%, respectively.[48]

NCCN Recommendations

T-PLL is an aggressive malignancy associated with rapid disease progression, and the majority of patients are symptomatic at the time of presentation. In a retrospective analysis of 81 patients with T-PLL, patients with inactive disease had a significantly longer OS than patients with active disease and among patients with symptomatic disease, the presence of B symptoms, low hemoglobin, low platelet count, lymphocyte doubling time of fewer than 3 months, and abnormal cytogenetics were associated with shorter OS.[45]

Given the poor prognosis associated with T-PLL, the NCCN Guidelines Panel recommends that patients should be enrolled in a clinical trial.

Observation is a reasonable approach until symptoms develop in the minority of patients who are asymptomatic with a more indolent course of disease. Systemic therapy with alemtuzumab-based regimens is recommended for patients with symptomatic disease (disease-related constitutional symptoms; symptomatic bone marrow failure; rapidly enlarging lymph nodes, spleen, and liver; increasing lymphocytosis; or extranodal involvement).[3] Monotherapy with IV alemtuzumab is the preferred primary treatment option.[32,33] Sequential therapy with FCM followed by IV alemtuzumab[30,31] or pentostatin in combination with alemtuzumab[23,26] are included as alternate treatment options for selected patients with bulky disease, splenomegaly, and hepatic involvement whose disease may not respond well to alemtuzumab monotherapy.

Allogeneic HCT should be considered for patients who achieve a CR or PR following initial therapy.[39-41,44,45] Autologous HCT may be considered, if a donor is not available and if the patient is not physically fit enough to

undergo allogeneic HCT.[47,48] However, it should be noted that there are no established response criteria based on the imaging studies for T-PLL and consensus criteria for response assessment have been proposed by the T-PLL International Study Group based on the evaluation of constitutional symptoms and the function of the hematopoietic system.[3]

At this time, the limited availability of data precludes any definitive recommendations for the management of relapsed disease. Based on the available data (discussed above), pentostatin (preferred regimen) [24,25] and ruxolitinib (other recommended regimen) [34] are included as options for the treatment of relapsed or progressive disease. Treatment with alternate regimens not used during first-line therapy is also an acceptable option for disease relapse following an initial response to therapy, disease not responding to initial therapy, or disease progression during initial therapy.

Loss of CD52 expression has been described as a mechanism of resistance to alemtuzumab treatment.[49,50] If CD52 expression is still positive at the time of relapse, retreatment with alemtuzumab with or without pentostatin can be considered for disease relapse after a period of remission following first-line therapy.

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 jirovecii* pneumonia (PJP) is recommended for all patients receiving alemtuzumab-based regimens. See *Supportive Care: Monoclonal Antibody Therapy and Viral Reactivation* in the algorithm.

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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).[1-3] 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 approximately 10% of the diagnosis for confirmed cases of PTCL or natural killer (NK)-cell/T-cell lymphomas (n = 1153).[4] While ATLL is rare in North America or Europe (≤2%), it has a higher prevalence in Asia (25%), with all cases from Asia originating in Japan. In the United States, 2148 cases were reported from 2001 to 2015, representing an overall rate of 0.06 per 100,000 population.[5]

The Lymphoma Study Group of the Japan Clinical Oncology Group (JCOG) has classified ATLL into four subtypes (smoldering, chronic, acute, or lymphoma) based on laboratory evaluations (eg, serum lactate dehydrogenase [LDH], hypercalcemia, lymphocytosis) and clinical features (eg, lymphadenopathy, hepatosplenomegaly, skin involvement).[6]

The smoldering (10%) and chronic (10%) subtypes are considered indolent, usually characterized by greater than or equal to 5% abnormal T-lymphocytes in the peripheral blood, and may have skin or pulmonary lesions (but no ascites or pleural effusion).[3] In addition, the smoldering subtype is also associated with a normal lymphocyte count, normal serum calcium level, LDH levels within 1.5 times upper limit of normal (ULN), and no involvement of the liver, spleen, central nervous system (CNS), bone, or gastrointestinal (GI) tract.[6] The chronic subtype is characterized by absolute lymphocytosis (≥4 x 10^9/L) with T lymphocytes greater than or equal to 3.5 x 10^9/L, normal calcium level, LDH levels within two times the ULN, and no involvement of CNS, bone, or GI tract; lymphadenopathy and involvement of liver and spleen may be present.[6]

The lymphoma subtype (20%) is characterized by the absence of lymphocytosis, less than or equal to 1% abnormal T-lymphocytes, and histologically proven lymphadenopathy with or without extranodal lesions.[3]

The acute subtype (60%) is characterized by elevated LDH levels, hypercalcemia (with or without lytic bone lesions), B symptoms, generalized lymphadenopathy, splenomegaly, hepatomegaly, skin involvement, and organ infiltration.[7] The acute subtype is associated with a rapidly progressive disease (PD) course and usually presents with leukemic manifestation and tumor lesions, and represents cases that are not classified as any of the other three subtypes above.[6]

Literature Search Criteria

Prior to the update of this version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) T-Cell Lymphomas, a literature search of the PubMed database was performed to obtain key literature in ATLL published since the last Guidelines update. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[8]

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; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

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.

Prognosis

The smoldering and chronic subtypes have a more favorable prognosis compared with the acute or the lymphoma subtypes.[4,6,9,10] In the analysis of 818 patients with ATLL (median age 57 years) from the Lymphoma Study Group of JCOG, the estimated 4-year overall survival (OS) rates for patients with acute, lymphoma, chronic, and smoldering subtypes were 5%, 6%, 27%, and 63%, respectively.[6] 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.[6] The poor prognosis of acute and lymphoma subtypes was also confirmed in another retrospective analysis that included 1665 patients with ATLL.[10] The median survival was 8 months and 11 months, respectively, for patients with acute and lymphoma subtypes compared to 32 months and 55 months, respectively, for those with chronic and smoldering subtypes. The corresponding 4-year OS rates were 11%, 16%, 36%, and 52%, respectively.[10]

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.[9] 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. In this study, 65% of patients died of acute ATL with a median time to transformation of 19 months, suggesting that most patients with indolent disease will eventually die of aggressive disease during their long-term disease course.[9]

Poor performance status, elevated LDH level, greater than or equal to four total involved lesions, hypercalcemia, and age greater than or equal to 40 years have been identified as major adverse prognostic factors based on data from a large number of patients.[11] Among patients with the chronic subtype, poor performance status, greater than or equal to four 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.[9] 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.

The International PTCL Project reported that the International Prognostic Index (IPI) was a useful model for predicting outcomes for patients with aggressive subtypes of ATLL.[4] Based on univariate analysis, presence of B symptoms, platelet count less than 150 x 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.[4] New prognostic models have been proposed for patients since IPI scores are not always predictive of ATLL outcomes.

A prognostic index for indolent ATLL (iATL-PI) was developed based on the soluble interleukin-2 receptor (sIL-2R) levels.[12] In a retrospective analysis of 248 patients with chronic or smoldering ATLL, iATL PI stratified patients into three 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 6 years and 2 years, respectively, for patients with an intermediate- or high-risk score. This prognostic index has to be validated in prospective trials.

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 three prognostic categories based on

Eastern Cooperative Oncology Group (ECOG) performance status, Ann Arbor stage, age, and serum calcium level at diagnosis.[13]

In a retrospective analysis of 807 patients with newly diagnosed acute or lymphoma subtypes, Ann Arbor stage, ECOG performance status, and three continuous variables (age, serum albumin, and sIL-2R) were independent prognostic factors and a prognostic index (ATL-PI) based on these variables stratified patients with acute and lymphoma subtypes into three risk groups (low, intermediate, and high) with a median survival of 16 months, 7 months, and 4 months, respectively.[14] The majority of patients included in the study were 70 years or older (not candidates for allogeneic hematopoietic cell transplant [HCT]) and this study excluded patients who were candidates for allogeneic HCT.

A modified prognostic index was developed for the risk stratification of patients 70 years or younger with aggressive ATLL who may benefit from upfront allogeneic HCT.[15] In a study of 1792 patients (70 years or younger) newly diagnosed aggressive ATLL treated with first-line chemotherapy, acute subtype, poor performance status, high sIL-2R levels (> 5,000 U/mL), high adjusted calcium levels (≥ 12 mg/dL), and high C-reactive protein (CRP) levels (≥ 2.5 mg/dL) were independent adverse prognostic factors of survival. The modified prognostic index stratified patients into 3 risk groups: low risk (scores of 0 and 1), intermediate risk (scores of 2 and 3) and high risk (scores of 4 and 5) with significantly different OS rates. The estimated 3-year OS rates were 36%, 23% and 7% respectively.[15] The estimated 3-year OS rate for patients who underwent allogeneic HCT was 40% in the intermediate-risk group and 27% in the high-risk group. The corresponding 3-year OS rates were 14% and 1% respectively for non-transplant candidates.

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%).[4] Bone marrow involvement (28%) and CNS involvement (10%) are also not uncommon.[4]

The presence of greater than or equal to 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.[6] 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.[7,16] These cytologic characteristics are most evident in the acute subtype of the disease.

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.[16,17] The immunophenotyping panel for flow cytometry should at minimum include the following markers: CD3, CD4, CD5, CD7, CD8, CD25, CD30 and TCRαß. The typical immunophenotype in most patients with ATLL involves mature CD4-positive T cells with expression of CD2, CD5, CD25, CD45RO, CD29, TCRαß and HLA-DR.[7,16] Most ATLL cells lack CD7 and CD26 and have a dim CD3 expression.[16] Rare cases are CD8+ or CD4/CD8 double positive or double negative.

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.[16] 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.[18]

CCR4 gain-of-function mutations are associated with long-term survival in patients treated with mogamulizumab without allogeneic HCT and assessment of CCR4 expression by immunohistochemistry may be useful for the identification of patients with *CCR4* gain-of-function mutations who may benefit from mogamulizumab-containing regimens.[19,20]

Integrated molecular analysis using targeted sequencing has identified recurrent mutations in a variety of genes involved in T-cell receptor and NF-κB signaling and other T cell-related pathways.[21-24] Acute and lymphoma subtypes were associated with higher frequencies of *TP53* and *IRF4* mutations as well as programmed death ligand 1 (PD-L1) amplifications and *CDKN2A* deletions compared with chronic and smoldering subtypes.[22] *STAT3* mutations were more characteristic of indolent subtype, with phosphorylated STAT3 expression significantly associated with better OS and progression-free survival (PFS) in the smoldering subtype, whereas *STAT3* mutation was not associated with clinical outcome.[23] *IRF4* mutations, PD-L1 amplifications and *CDKN2A* deletions are associated with a worse prognosis in indolent subtypes.[22,24] These findings suggest that ATLL subtypes could be further classified into molecularly distinct subsets with different prognosis and the use of next-generation sequencing (NGS) may be useful to identify the presence of the recurrent gene mutations associated with inferior prognosis.

HTLV-1 integration patterns have been reported to have clinical and prognostic implications for ATLL.[3,25] HTLV-1 serology is essential to distinguish ATLL from cutaneous T-cell lymphomas, including mycosis fungoides (MF), and PTCL, especially in endemic areas.[26] HTLV-1 serology should be assessed by enzyme-linked immunoassay (ELISA) and, if positive, confirmed by western blot. If the result from western blot is indeterminate, then polymerase chain reaction (PCR) analysis for HTLV-1 can be performed. Monoclonal integration of HTLV-1 proviral DNA occurs in all cases of ATLL.

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 complete blood count (CBC) with differential and complete metabolic panel (serum electrolyte levels, calcium, creatinine, and blood urea nitrogen) and measurement of serum LDH, CRP and sIL-2R 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.[27-29] 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.[30] Human leukocyte antigen (HLA) typing is recommended, if considering allogeneic hematopoietic cell transplant (HCT).

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.[16,26] 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 the spleen or liver, and decrease in the involvement of peripheral blood, bone marrow, and skin.[16,26]

The response is categorized as a complete response (CR; defined as complete disappearance of all clinical, microscopic, and radiographic evidence of disease and absolute lymphocyte count, including flower cells, <4 x 10^9/L in the peripheral blood), partial response (PR; defined as ≥50% reduction in the sum of the products of the greatest diameters of measurable disease without the appearance of new lesions, no increase in spleen or liver size, ≥50% reduction in skin involvement, and ≥50% reduction in absolute lymphocyte counts in peripheral blood), stable disease (SD; failure to achieve CR or PR with no 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).[16] 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 uncertified complete response (CRu), defined as greater than or equal to 75% reduction in tumor size but with a residual mass after treatment, with an absolute lymphocyte count, including flower cells, of less than 4 x 10^9/L. The usefulness of PET or PET/CT has not been evaluated in the response assessment of patients with ATLL.

Treatment Options

The optimal chemotherapy regimen is not yet established and the efficacy of long-term treatment is limited since patients with ATLL have either been underrepresented or excluded from the prospective clinical trials evaluating treatment options for T-cell lymphomas. Enrollment in a clinical trial is the preferred treatment option for all patients with newly diagnosed and relapsed/refractory disease. The chemotherapy regimens included in the NCCN Guidelines are based on limited available data (mostly from retrospective analyses as discussed below) and institutional preferences. Screening and treatment (if needed) for strongyloidiasis and *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis with sulfamethoxazole/trimethoprim or equivalent are recommended for all patients.[16]

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 interferon-alfa (IFN-alfa) has been reported in a number of small studies and case reports.[31-35] Among patients with primarily treatment-naïve aggressive ATLL, zidovudine in combination with IFN-alfa resulted in an overall response rate (ORR) of 58% to 80% and CR rates of 20% to 50%.[31,32,35] Outcomes with this therapy were poorer for patients with previously treated relapsed/refractory disease, with ORR 17% to 67% (nearly all PRs).[33,34]

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 [cyclophosphamide, doxorubicin, vincristine, and prednisone] in 86% of cases), or chemotherapy followed by maintenance antiviral therapy

(n = 55).[36] 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.[36] 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%).[36] 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.[36]

In the subgroup analysis by first-line treatment regimen, antiviral therapy resulted in significantly longer median OS (17 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.[36] 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-like regimens) or combined therapy with chemotherapy and antiviral agents (zidovudine and IFN-alfa; given concurrent or sequential to chemotherapy or deferred).[37] The median OS among patients with the acute and lymphoma subtypes was 8 months and 10 months, respectively. The use of antiviral treatments (at any point in the study) was associated with significant OS benefit for both the subgroups with acute and lymphoma ATLL.[37] 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.[37]

Combination chemotherapy with CHOP has resulted in an ORR of 64% to 88% (CR rates of 18%–25%) with median OS ranging from approximately 8 to 12 months.[13,36,38] 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.[36] 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%; $P = .009$).[36]

In a small phase II trial conducted by the AIDS Malignancy Consortium in 19 patients with aggressive ATLL, EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) 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.[39] 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. The use of dose-adjusted EPOCH in combination with bortezomib and antiviral therapy (raltegravir) resulted in an ORR of 67% in patients with acute and lymphoma subtypes.[40] After a follow-up of greater than 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; however, prospective evaluations are needed.[41]

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).[42] 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 14%.[42]

In a randomized phase III trial (JCOG9801), VCAP (vincristine, cyclophosphamide, doxorubicin, and prednisone)-AMP (doxorubicin, ranimustine, and prednisone)-VECP (vindesine, etoposide, carboplatin, and prednisone) resulted in significantly higher CR rate compared to CHOP-14 (40% vs. 25%; *P* = .02), but the median PFS (7 vs. 5 months, respectively), median OS (13 vs. 11 months, respectively),1-year PFS rate (28% vs. 16%) and 3-year OS rate (24% vs. 13%) were not significantly different between the treatment arms.[43] 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 report from the ATL-PI Project from Japan that included 1250 patients with acute or lymphoma subtype, CHOP-21 or CHOP-14 was the most commonly used regimen (n = 579; 50%) followed by VCAP-AMP-VECP (n = 365; 31%) and modified EPOCH (n = 42; 4%).[10] The findings from a supplementary analysis of the phase III trial (JCOG9801) that evaluated the benefit based on the risk-group (as identified by the ATL-PI) confirmed that while VCAP-AMP-VECP is a suitable regimen for the intermediate-risk group, it was associated with only a modest benefit in the low-risk group.[44]

VCAP-AMP-VECP and ATL-G-CSF are not recommended in the NCCN Guidelines since vindesine and ranimustine are not available in the United States.

NCCN Recommendations

Observation is appropriate for patients with asymptomatic smoldering ATLL (no skin lesions or opportunistic infections). In patients with symptomatic smoldering ATLL, skin-directed therapies (as recommended for patients with MF or Sézary syndrome [SS] in the NCCN Guidelines for Primary Cutaneous Lymphomas) are appropriate for patients with skin lesions and zidovudine in combination with IFN-alfa is an option for patients those with tumor lesions.

Treatment options for patients with chronic ATLL is based on the risk stratification using the iATL-PI (discussed above).[12] Zidovudine in combination with IFN-alfa is a treatment option for all patients with chronic ATLL (irrespective of the risk score) whereas combination chemotherapy is an option only for patients with high-risk disease (sIL-2R >6000 U/mL).

Combination chemotherapy is recommended for patients with the acute or lymphoma subtype. Zidovudine in combination with IFN-alfa is a first-line therapy for patients with acute subtype whereas this combination is not

considered effective for patients with lymphoma subtype.[36] 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 to or is progressing on zidovudine and IFN-alfa, treatment should be stopped.

Dose-adjusted EPOCH is included as a preferred chemotherapy regimen.[37,39] CHOEP or hyper-CVAD are included as alternative options under other recommended regimens.[32,34,40] CHOP may be an appropriate treatment option for patients unable to tolerate intensive regimens or for those with non–CD30-positive ATLL.[11]

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.[45] The results of the ECHELON-2 trial established the superiority of brentuximab vedotin (BV) in combination with cyclophosphamide, doxorubicin, and prednisone (CHP) compared with CHOP in patients with systemic anaplastic large cell lymphoma (ALCL) and BV in combination with CHP is FDA approved for the initial treatment of systemic ALCL, CD30-positive PTCL, not otherwise specified and CD30-positive angioimmunoblastic T-cell lymphoma (AITL).[46] The ECHELON-2 trial also included seven patients with ATLL and based on the results of this trial, the panel has included BV + CHP as a preferred treatment option for patients with CD30-positive ATLL.

Second-line Therapy

Arsenic trioxide in combination with IFN-alfa has been shown to be an effective treatment option for relapsed or refractory disease despite significant toxicity.[47,48] Alemtuzumab, bortezomib, and pralatrexate also have demonstrated activity as single agents in a small series of patients with relapsed/refractory ATLL.[49-52]

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%.[50] The median PFS and OS were 4 months and 20 months, respectively. Neutropenia, leukopenia, lymphopenia, and thrombocytopenia were the most common grade greater than or equal to three adverse events occurring in 65%, 38%, 38%, and 23% of patients, respectively.

Mogamulizumab (a humanized anti-CCR4 monoclonal antibody) is approved for the treatment of patients with relapsed or refractory CCR4-positive ATLL in Japan.[53-55] The safety and efficacy of mogamulizumab for patients with relapsed/refractory ATLL was demonstrated in a prospective randomized study outside of Japan.[56] In this study, 71 patients with relapsed or refractory ATLL (acute, chronic and lymphomas subtypes) were randomized to either mogamulizumab (n = 47) or an investigator choice (IC) regimen (n = 24; GEMOX [gemcitabine and oxaliplatin], DHAP [dexamethasone, cytarabine and cisplatin], or pralatrexate).[56] Patients in the IC arm were permitted crossover to mogamulizumab upon disease progression. The confirmed ORR as assessed by the investigator, and independent review were higher for patients treated with mogamulizumab (15% and 11%, respectively) than for those treated with IC regimen (0% for both). The best ORR as assessed by independent review was 28% for mogamulizumab compared to 8% for IC regimen, and the best ORR as assessed by investigator review was 34% and 0%, respectively, for mogamulizumab and IC

regimen. Responses to mogamulizumab were seen across all ATLL subtypes (the best response rates were 71%, 32%, and 24%, respectively, for chronic, lymphoma, and acute subtypes). Infusion reactions (47%), drug eruption (19%), thrombocytopenia (13%), and anemia (11%) were the most common adverse events in the mogamulizumab arm.

The development of cutaneous adverse reaction (a drug-induced skin eruption or mogamulizumab-associated skin rash) that has variable clinical and pathologic features (and can mimic CTCL) has been identified as a predictor of efficacy of mogamulizumab treatment.[57,58] Skin biopsy (with adequate immunohistochemical stains and clonality assessment) is recommended to rule out disease progression in patients experiencing drug-induced skin eruptions or mogamulizumab-associated skin rash.[59,60]

Allogeneic Hematopoietic Cell Transplant

Available evidence mostly from retrospective studies suggest that allogeneic HCT may be associated with long term survival in some patients with ATLL,[61-69] suggesting a contribution of graft-versus-leukemia/lymphoma (GVL) effect.[70-72]

In a retrospective analysis of 386 patients with ATLL who underwent allogeneic HCT (related or unrelated) (n = 386), after a median follow-up of 41 months, the 3-year OS rate was 33% and the incidence of transplant-related mortality (TRM) was 43%, which was mainly due to infectious complications and organ failure.[66] 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.

In another retrospective study of 586 patients with ATLL (majority of patients had either acute [57%] or lymphoma [28%] subtypes), the use of myeloablative conditioning or reduced intensity conditioning (RIC) regimens resulted in similar outcomes with allogeneic HCT.[67] The median OS (survival measured from time of HCT) was 9.5 months and 10 months, respectively for patients who received myeloablative conditioning and RIC. The 3-year OS rates were 39% and 34% respectively. The 3-year cumulative incidence of TRM was 38% and 33%, respectively, for myeloablative conditioning regimens and RIC regimens. Patients who received RIC regimens were older than those who received myeloablative conditioning regimens (median age, 57 vs. 49 years). 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.[67] 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.

In the systematic review and meta-analysis that summarized the results of all the retrospective studies that have assessed the efficacy of allogeneic HCT in 1757 patients with ATLL, the pooled CR, OS, and PFS rates following allogeneic HCT were 73%, 40%, and 37%, respectively.[73] Pooled relapse and non-relapse mortality rates were 36% and 29%, respectively. There was high rate of heterogeneity among the studies included in this meta-analysis and with the exception of study from the EBMT registry,[68] most of the studies included patients undergoing allogeneic HCT in Japanese medical centers. A more recent single institution study has also reported favorable outcomes of allogeneic HCT with moderate rates of TRM and graft-versus-host disease (GVHD) in 17 non-Japanese patients with ATLL.[74]

The results of a retrospective analysis showed that induction of GVL effect via donor lymphocyte infusion (DLI) may provide long-lasting remission in

selected patients with relapsed ATLL.[75] 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.[76] 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.[77] 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

Continuation of the prior therapy is recommended for all patients who achieve an initial response to first-line therapy (CR, uncertified PR, or PR at 2 months following start of treatment). Allogeneic HCT should be considered (if a donor is available) for patients with high-risk chronic subtype, acute or lymphoma subtype that is responding to first-line or second-line therapy. Among patients with acute and lymphoma subtypes, the modified prognostic index (discussed above) identified allogeneic HCT as a statistically significant favorable prognostic factor for OS for patients with intermediate and high-risk scores.[15]

Combination chemotherapy regimens (used for first-line therapy) is recommended for patients with symptomatic smoldering subtype that is not responding to initial therapy (persistent disease or has disease progression at 2 months from start of treatment).

Second-line therapy is recommended for patients with high-risk chronic subtype, acute or lymphoma subtype that is not responding to first-line therapy. Alternate regimen not previously used for first-line therapy is an appropriate option for patients with low- or intermediate-risk chronic subtype or acute subtype that is not responding to initial therapy.

Lenalidomide, brentuximab vedotin and mogamulizumab are included as preferred treatment options for second-line therapy. Brentuximab vedotin is an option for patients with CD30-positive relapsed/refractory disease based on the extrapolation of data from clinical trials that has demonstrated its efficacy in relapsed/refractory CD30-positive PTCL.[78] Mogamulizumab is not approved by the U.S. Food and Drug Administration (FDA) for the treatment of relapsed or refractory ATLL. Mogamulizumab (off-label use) is also included as a preferred single-agent second-line therapy option for relapsed or refractory ATLL, based on the results of the prospective randomized study (outside of Japan).[56] Mogamulizumab therapy for ATLL prior to allogeneic HCT has been significantly associated with an increased risk of GVHD-related mortality and should be used with caution in patients with ATLL who are eligible for or proceeding directly to allogeneic HCT.[79,80]

Arsenic oxide, alemtuzumab, bortezomib, or pralatrexate are included as alternate monotherapy options (other recommended regimens) based on limited available data as discussed above.[49-52] 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. The risk of Stevens-Johnson syndrome associated with pralatrexate may be higher in patients with ATLL compared to those with PTCL.[51] Belinostat (histone deacetylase inhibitor) has shown single-agent activity in patients with relapsed or refractory PTCL and is FDA approved the treatment of relapsed or refractory PTCL.[81] Belinostat is included as an option (off-label use; other recommended regimens) for relapsed/refractory ATLL.

The results of retrospective analysis confirmed that RT was a safe and effective palliative treatment of localized lesions.[82] RT is also included as an option for selected patients with localized, symptomatic disease. The

combination chemotherapy regimens included in the NCCN Guidelines for second-line therapy are based on institutional preferences. 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. DHAP and GEMOX regimens were used as control arms in the aforementioned prospective study of mogamulizumab for patients with relapsed/refractory ATLL and these regimens are included as options (other recommended regimens) for relapsed or refractory ATLL.[56]

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Hepatosplenic T-Cell Lymphoma

Hepatosplenic T-cell lymphoma (HSTCL) is a rare lymphoproliferative disorder associated with an aggressive clinical course and a worse prognosis.[1-3] HSTCL accounts for less than or equal to 2% of all cases of T-cell lymphomas diagnosed worldwide and in up to 20% of cases develops in the setting of chronic immune suppression or immune dysregulation, particularly inflammatory bowel disease (IBD), hematologic malignancies, and previous solid organ transplant.[4-6] The concomitant use of TNF-□ inhibitors and thiopurine-based immunomodulators has been identified as a risk factor for developing HSTCL among patients with IBD.[7,8]

HSTCL is most often characterized by spleen, liver, and bone marrow involvement. Lymphadenopathy is uncommon and patients frequently present with systemic symptoms, hepatosplenomegaly, cytopenias, and sometimes hemophagocytic lymphohistiocytosis (HLH).[9,10] Clinical presentation is highly non-specific and high index of suspicion is required to make the diagnosis. In the majority of cases, the neoplastic cells typically arise from lymphocytes having the surface expression of TCRδ and TCRɣδ.[6,11,12] In rare cases, neoplastic cells may express TCRαβ.[13-15] TCRɣδ variant has a male predominance with a median age of 35 years, whereas TCRαβ variant occurs more commonly in females >50 years.[4] Both are considered as immunophenotypic variants of the same disease and are managed in the same way.

Literature Search Criteria

Prior to the update of this version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for T-Cell Lymphomas, a literature search of the PubMed database was performed to obtain key literature in HSTCL published since the previous Guidelines update. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes 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; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The data from key PubMed articles 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.

Diagnosis

The diagnosis of HSTCL is most frequently established by a core needle biopsy of a bone marrow and/or liver with adequate immunophenotyping (either by immunohistochemistry [IHC] or cell surface marker analysis by flow cytometry) as well as molecular studies.[5] Examination of peripheral blood smear, bone marrow aspirate, and fine-needle aspiration (FNA) biopsy of liver may be helpful but are not solely sufficient for the diagnosis. Splenectomy may be required in some cases and core needle biopsy of spleen could be considered in some cases, in centers of excellence with expertise in performing this procedure.

The interpretation of cytotoxic cells seen on the bone marrow biopsy specimen may be difficult and multiple biopsies may be needed prior to making a definitive diagnosis, since biopsy results may be inconclusive. Additional liver biopsy may be helpful to confirm the diagnosis. Liver biopsy with adequate immunophenotyping should be reviewed by a hematopathologist.[17]

HSTCL is typically characterized by the following immunophenotype: CD2+, CD3+, CD4-, CD5-, CD8+/-, CD56+/-, TCRγδ+, TIA1+, TdT, and granzyme B-.[18] An IHC panel to evaluate for HSTCL typically includes CD20, CD3, CD10, Ki-67, CD5, CD30, CD2, CD4, CD8, CD7, CD56, EBER-ISH, TCRβ, TCRδ, TIA-1, and granzyme B. Cell surface marker analysis by flow cytometry often includes kappa/lambda, CD45, CD3, CD5, CD19, CD10, CD20, CD30, CD4, CD8, CD7, CD2; TCRδ, TCRαβ, or TCRγδ.[17]

Molecular analysis or other assessment of clonality can be used to detect clonal *TCR* gene rearrangements. The identification of *TCRγ* gene rearrangement on molecular analysis reflects the clonality of the T cells. However, the molecular clonality studies cannot be used to define the T-cell subtype (αβ vs. γδ) since *TCRβ* and *TCRγ* gene rearrangements may be seen in both αβ and γδ HSTCL.[14]

Isochromosome 7q and trisomy 8 are the most common chromosomal abnormalities in HSTCL.[6,19-23] Isochromosome 7q and ring chromosome 7 are associated with loss of 7p and amplification of 7q resulting in altered expressions of several oncogenes located on chromosome 7 (*CHN2, ABCB1*, and *PPP1R9A*).[24] Gene expression profiling studies have identified distinct molecular signatures that distinguish HSTCL from other T-cell lymphomas.[25-27] In a whole exome sequencing study on 68 primary HSTCL tumors, mutations in chromatin-modifying genes including *SETD2, INO80*, and *ARID1B* (occurring almost exclusively in HSTCL compared to other T-cell lymphoma subtypes*)* were present in 62% of cases.[27] In addition, *STAT5B, STAT3*, and *PIK3CD* mutations have also been identified in 31%, 9%, and 9% of cases, respectively.[27] *STAT3* and *STAT5* mutations, however, are not unique to HSTCL and have also been identified in large granular lymphocytic leukemia (LGLL) and other T-cell lymphoma subtypes.[28-31]

It is essential to consider other T-cell/natural killer (NK)-cell neoplasms with significant overlapping features with HSTCL in the differential diagnosis (γδ-T-cell LGLL, T-cell lymphoblastic leukemia, primary cutaneous-γδ-T-cell lymphoma, intestinal monomorphic epitheliotropic intestinal T-cell lymphoma, aggressive NK-cell leukemia, Epstein-Barr virus [EBV]-positive T-cell lymphoma, and NK-cell lymphoproliferative diseases of childhood, and, rarely, other T-cell lymphomas with expression of TCRγδ).[17,32] Fluorescence in situ hybridization (FISH) and karyotype for the identification of isochromosome 7q and trisomy 8 and next-generation sequencing (NGS) panel including *STAT3*, *STAT5B*, *PIK3CD*, *SETD2, INO80*, and *TET3* would be useful for the differential diagnosis for HSTCL.[22,23,27]

Non-neoplastic, transient conditions leading to an increase in γδ T-cells with a similar phenotype, including infections such as ehrlichiosis and other tick-borne diseases, should also be considered in the differential diagnosis of HSTCL.[33,34]

Workup

The initial workup should include comprehensive medical history and physical examination including full skin examination and routine laboratory studies (bone marrow biopsy ± aspirate, complete blood count [CBC] with differential, comprehensive metabolic panel, and assessment of serum uric acid and lactate dehydrogenase [LDH]). Fluorodeoxyglucose (FDG)-PET/CT and/or CT of chest/abdomen/pelvis with contrast of diagnostic quality are essential for workup. In the absence of lymphadenopathy, normal FDG uptake in lymph nodes are pertinent negative findings on PET/CT scan that could differentiate HSTCL from other lymphomas.[35] CT scan of the neck and CT or MRI of the head may be useful in some cases.

Multigated acquisition (MUGA) scan or echocardiogram is recommended under certain circumstances. Quantitative polymerase chain reaction (PCR) for EBV and cytomegalovirus (CMV) reactivation as well as serology testing for the HIV and human T-cell lymphotropic virus (HTLV-1) may be useful in selected cases.

Human leukocyte antigen (HLA) typing is recommended for all patients eligible for transplant, since HSTCL is associated with a poor outcome in the absence of a consolidative allogeneic hematopoietic cell transplant (HCT). Early referral to transplant is advisable for planning purposes.[15]

Hemophagocytic Lymphohistiocytosis

HLH is a rare but potentially life-threatening hyper-inflammatory syndrome and it is most often associated with an underlying hematologic malignancy, especially T-cell lymphomas in adults.[9] HSTCL should be considered in the differential diagnosis when evaluating patients presenting with symptoms associated with HLH.

Optimized HLH inflammatory (OHI) index can be considered to simplify the diagnosis of HLH in patients with hematologic malignancies.[36] Diagnostic workup to confirm the lymphoma subtype and prompt initiation of treatment for underlying T-cell lymphoma (preferably with etoposide- and steroid-containing regimens) is often required.[36,37]

Treatment

HSTCL are underrepresented in prospective clinical studies and treatment recommendations are based on the evidence mainly from small case reports or case series and single-center retrospective studies.[5] Outcomes are poor with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-based chemotherapy regimens. More intensive non–CHOP-based chemotherapy regimens like ICE (ifosfamide, carboplatin, and etoposide) or IVAC (ifosfamide, etoposide, and cytarabine) have been associated with potentially improved outcomes compared with CHOP or a CHOP-like regimen.[38-41] Purine analogs (pentostatin or cladribine) either as monotherapy or in combination with alemtuzumab have also demonstrated modest activity.[42-47]

Few studies have reported improved survival outcomes with autologous or allogeneic HCT as consolidation therapy for patients with disease in first or second remission.[40,48-50] Autologous HCT has also been shown to provide some benefit for patients when an allogeneic HCT is not feasible.[40] Some studies have also reported that graft-versus-lymphoma effect associated with allogeneic HCT may result in long-term survival in a significant proportion of patients with HSTCL and active disease at the time of transplant was not necessarily associated with poor outcomes.[48,49] In a U.S. multicenter collaborative study that evaluated the outcomes of HCT in 53 patients with HSTCL, the median OS and progression-free survival (PFS) were 79 months and 54 months, respectively, for the entire study cohort with no significant differences in OS (P = .245) or PFS (P = .365) between autologous and allogeneic HCT.[50] The 3-year cumulative incidence of relapse rates were 35% and 43%, respectively, for autologous and allogeneic HCT. The 3-year cumulative incidence of non-relapse mortality (NRM) rates were 16% and 14%, respectively. The efficacy of allogeneic HCT in relapsed or refractory disease has also been demonstrated in several case reports.[51-53]

An individual-level meta-analysis (which represents the largest aggregation of all published studies and case reports so far; 166 patients with a diagnosis of HSTCL) compared the response rates and overall survival (OS) outcomes of 84 patients with HSTCL treated with CHOP or CHOP-like regimens (n = 50) or non–CHOP-based regimens, specifically those containing cytarabine, platinum, and etoposide (n = 34).[41] Non–CHOP-based regimens were associated with an overall response rate of 82% compared with 52% for CHOP or CHOP-like regimens (P = .006). The median survival was 37 months and 18 months, respectively (P =

.00014). The use of a non–CHOP-based regimen was a significant predictor of higher response rate (*P* = .049) and improved survival (*P* = .026). This study also demonstrated a benefit for HCT on survival and the superiority of allogeneic HCT over autologous HCT. The 2-year survival rate was 12% for patients who did not receive HCT compared to 41% and 56%, respectively, for those who received autologous HCT and allogeneic HCT.

NCCN Recommendations

The optimal treatment approach remains undefined given the absence of data from prospective randomized clinical studies. Clinical trial, if an appropriate one is available, is the preferred initial treatment option for all patients with HSTCL. The goal of initial therapy is to induce complete or near complete response to allow successful bridging to HCT, preferably an allogeneic HCT. Since HSTCL is non-nodal, Lugano response criteria do not apply for response assessment and PET-negative response should be confirmed by bone marrow biopsy and in selected cases by liver biopsy.

CHOP is not considered adequate therapy. In the absence of data from prospective and randomized studies, the results of the aforementioned individual-level meta-analysis support the use of induction therapy with non–CHOP-based regimens followed by consolidation with allogeneic HCT as an effective treatment approach (associated with improved survival) for all eligible patients with HSTCL.[41]

ICE is included as the preferred regimen for induction therapy since this is used in the majority of NCCN Member Institutions. Other intensive induction therapy regimens such as DHA (dexamethasone and cytarabine) with cisplatin or oxaliplatin, dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), IVAC, and hyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine may also be appropriate and are included as options under other recommended regimens.[40,41]

The phase III randomized trial (ECHELON-2) showed that brentuximab vedotin (BV) in combination with CHP (cyclophosphamide, doxorubicin, and prednisone) was superior to CHOP for the treatment of patients with previously untreated CD30-positive peripheral T-cell lymphoma (PTCL) (defined in ECHELON-2 as CD30 expression on ≥10% of cells), resulting in significantly improved PFS and OS.[54] The survival benefit was clearly established for the subset of patients with anaplastic large cell lymphoma (ALCL), but the benefit was less clear across other histologic subtypes.[54] Based on the results of the ECHELON-2 trial, BV in combination with CHP was approved by the FDA as a first-line therapy for patients with untreated systemic ALCL or other CD30-expressing subtypes (≥1% CD30 expression) including PTCL, not otherwise specified (NOS) and angioimmunoblastic T-cell lymphoma (AITL).

Patients with HSTCL were eligible for the ECHELON-2 study but no patients were enrolled. Given that BV + CHP has demonstrated activity in CD30+ subtypes of PTCL, BV + CHP is included as an alternate treatment option with a category 2B recommendation for patients with CD30+ HSTCL. Alemtuzumab + pentostatin and CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone) are also included as alternative options (useful in certain circumstances).

Consolidation therapy with allogeneic HCT is recommended for eligible patients with complete response or partial response after initial induction therapy or second-line therapy.[41,46,49,50] Consolidation therapy with autologous HCT can be considered if a suitable donor is not available or for patients who are ineligible for allogeneic HCT.[40,50]

Patients with disease not responding to primary treatment or those with progressive disease should be treated with alternate induction therapy

regimens before receiving treatment for relapsed/refractory disease.[5] Purine analogs or regimens recommended for second-line therapy for PTCL-NOS may be appropriate for the treatment of patients with relapsed/refractory HSTCL. Responses have been observed with alemtuzumab, pralatrexate, duvelisib and ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin).[5]

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Extranodal Natural Killer/T-Cell Lymphomas, Nasal Type

Overview

Natural killer (NK)/T-cell lymphomas are a rare and distinct subtype of non-Hodgkin lymphomas (NHL) that are predominantly extranodal. The majority of extranodal NK/T-cell lymphomas (ENKL) are of nasal type, often localized to the upper aerodigestive tract including the nasal cavity, nasopharynx, paranasal sinuses, tonsils, hypopharynx, and larynx.[1,2] However, ENKL can also have an extranasal presentation (ENKL of non-upper aerodigestive tract), with skin, testis, and gastrointestinal tract being the most common sites of extranasal involvement or metastatic disease.[3-6]

ENKL, non-nasal type is associated with more unfavorable prognostic factors and poorer prognosis than ENKL, nasal type.[3,6] A greater proportion of the patients with ENKL, non-nasal type present with advanced-stage disease (68% vs. 27%), mass greater than 5 cm (68% vs. 12%), greater than 2 extranodal sites (55% vs. 16%), elevated lactate dehydrogenase (LDH) levels (60% vs. 45%), and B symptoms (54% vs. 39%).[3] ENKL, non-nasal type is associated with shorter median overall survival (OS; 4 months vs. 19 months for ENKL, nasal type) and inferior OS rate (5-year OS rate was 34% vs. 54% for patients with ENKL, nasal type).[3,6]

The increasing use of non–anthracycline-based chemotherapy regimens that are more specific for ENKL has resulted in significant improvement in survival rates. 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.

Literature Search Criteria

Prior to the update of this version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for T-Cell Lymphomas, a literature search of the PubMed database was performed to obtain key literature in ENKL published since the last Guidelines update. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[7]

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; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

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.

Diagnosis

The most common clinical features of ENKL, nasal type include nasal obstruction or nasal bleeding. Histopathologic features in most cases of ENKL are characterized by diffuse lymphomatous infiltrates, angiocentricity, and angiodestructive growth patterns resulting in tissue ischemia and necrosis, and ulceration of mucosal sites.[1] 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 sample. 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.

The typical immunophenotype for NK-cell ENKL is CD20-, CD2+, cCD3□+ (surface CD3-), CD4-, CD5-, CD7-/+, CD8-/+, CD43+, CD45RO+, CD56+,

TCRαβ-, TCRδγ-, Epstein-Barr virus (EBV)-Epstein-Barr encoding region (EBER)+, and cytotoxic granule proteins positive (eg, TIA-1+, granzyme B+).[3] For NK-cell lineage, *TCR* and immunoglobulin gene represent germline sequences. The typical immunophenotype for T-cell lineage is CD2+, cCD3□+, surface CD3+, variable CD4/CD5/CD7/CD8, TCRαβ+ or TCRδγ+, EBV-EBER+, and cytotoxic granule proteins positive.

Adequate immunophenotyping is essential to confirm the diagnosis. The initial immunohistochemistry (IHC) panel should include cytoplasmic CD3□□(cCD3□), CD2, CD5, CD56 and TIA1. Additional recommended markers for the IHC panel include CD20 for B-cell lineage; CD4, CD7, CD8, granzyme B, TCRβ, TCRδ 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).[1] EBV-negative ENKL is very rare and has not been fully investigated.[8] A negative EBER-ISH result should prompt hematopathology review for an alternative diagnosis.

Clonal *TCR* gene rearrangements have been found in up to one third of cases with ENKL, nasal type.[3] Molecular analysis to detect clonal *TCR* gene rearrangements may be useful under certain circumstances. Ki-67 expression has been reported to be prognostic in patients with stage I/II ENKL, nasal type.[9,10] High Ki-67 expression (≥65%) was associated with a shorter OS and disease-free survival (DFS). In a multivariate analysis, Ki-67 expression and primary site of involvement were found to be independent prognostic factors for both OS and DFS.[9]

Workup

The initial workup should include a history and physical (H&P) examination with attention to node-bearing areas (including Waldeyer's ring), testicles and skin, complete ear, nose, and throat (ENT) evaluation of nasopharynx, as well as evaluation of B symptoms and performance status. Laboratory tests should include a complete blood count (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 multigated acquisition (MUGA) scan or echocardiogram should be performed if treatment with anthracycline or anthracenedione is being considered.

Bone marrow involvement is uncommon at diagnosis and occurs in less than 20% of patients within the disease course.[11,12] PET/CT has demonstrated satisfactory predictive performance in terms of staging, and the use of routine bone marrow biopsy is not essential in patients with early-stage disease.[13] Bone marrow biopsy is recommended to confirm bone marrow involvement in patients with advanced-stage disease. Morphologically negative biopsies should be evaluated by EBER-ISH and, if positive, should be considered involved.[11,14-16]

Ocular and central nervous system (CNS) involvement have been described (although both are very rare).[17-20] CNS involvement at the time of initial diagnosis is associated with a poor prognosis, and autologous hematopoietic cell transplant (HCT) may be associated with improved survival outcome in patients with CNS involvement.[18,20] Ophthalmologic exam and lumbar puncture with cerebrospinal fluid (CSF) analysis may be useful in certain circumstances.

Prognosis

The use of International Prognostic Index (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 four risk groups (low risk, low-intermediate risk, intermediate-high risk, and high risk) with different survival outcomes based on the presence or absence of four prognostic factors (B symptoms, disease stage, LDH levels, and regional lymph node involvement).[21] Most patients had received anthracycline-based chemotherapy regimens with or without radiation therapy (RT).

The prognostic index of natural killer lymphoma (PINK) is used for the risk stratification of patients with ENKL treated with non–anthracycline-based chemotherapy.[22] 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 documented data for EBV-DNA, detectable EBV-DNA measured by quantitative polymerase chain reaction (PCR) was a significant predictor of OS. Based on these risk factors, PINK stratified patients into three 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 three 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. Vitamin D deficiency is an independent prognostic factor for inferior progression-free survival (PFS) and OS in patients with ENKL. The addition of vitamin D deficiency to the PINK-E scoring system had a superior prognostic significance compared PINK-E alone for PFS.[23,24]

EBV-DNA viral load correlates well with clinical stage, tumor burden, response to therapy, and survival.[25-28] Plasma EBV-DNA greater than or equal to 6.1×10^7 copies/mL at presentation has been associated with an inferior DFS.[25] Circulating EBV-DNA in whole blood and plasma (pre- or post-treatment) has been shown to be a good predictor of response, survival, and early relapse in patients with ENKL, nasal type treated with asparaginase- or pegaspargase-based chemotherapy.[29-34] In the phase II study from the NK-Cell Tumor Study Group, the overall response rate (ORR) was significantly higher in patients with less than 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 less than 10^4 copies/mL of EBV-DNA in plasma (95% vs. 29%; $P = .002$).[30] In addition, the incidence of grade 4 non-hematologic toxicity was significantly higher among patients with greater than or equal to 10^5 copies/mL of EBV-DNA in whole blood (100% vs. 29%; $P = .007$) and in patients with greater than or equal to 10^4 copies/mL of EBV-DNA in plasma (86% vs. 26%; $P = .002$). Pre-treatment EBV-DNA in plasma was also independently associated with advanced stage and poor PFS in multivariate analysis, suggesting that EBV-DNA level in the plasma has better prognostic value than that in whole blood.[34]

Measurement of EBV-DNA viral load by quantitative PCR is useful in the diagnosis and often in the monitoring of the disease. 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

RT is an important component of initial treatment and RT with or without chemotherapy has been effective in achieving higher ORR and complete response (CR) rates compared to chemotherapy alone in patients with early-stage ENKL.[3,35-41]

Early or up-front RT at doses of greater than or equal to 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.[38] 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 greater than or equal to 54 Gy, compared with 46% and 33%, respectively, for patients treated with RT doses of less than 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).

Involved-site RT (ISRT) is recommended as the appropriate field as it limits the volume of RT to the region of involvement only.[42] An ISRT dose of 50 to 55 Gy is recommended when used alone as primary treatment and 45 to 56 Gy is recommended when used in combination with chemotherapy. When ISRT is used alone, the clinical target volume (CTV) should encompass the involved region as defined by contrast-enhanced MRI and contrast-enhanced 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. In instances when chemotherapy was given prior to ISRT and has produced a CR, the CTV should include at least the prechemotherapy gross tumor volume (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.

The use of intensity-modulated RT (IMRT) has been associated with favorable locoregional control and improved survival outcomes (OS and PFS) with mild toxicity in patients with early-stage disease.[43,44]

Combination Chemotherapy

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.[45] Retrospective comparative studies have shown that asparaginase-based or pegaspargase-based regimens are associated with superior efficacy compared to the conventional anthracycline-based regimens.[40,46,47] Asparaginase-based chemotherapy regimens resulted in higher response rates than non–asparaginase-based chemotherapy regimens, although there were no significant differences in PFS or OS rates between asparaginase-based and non–asparaginase-based chemotherapy regimens.[40]

The SMILE regimen (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) or modified SMILE regimen (dexamethasone, methotrexate, ifosfamide, pegaspargase and etoposide; a single dose of pegaspargase is substituted for 7 doses of asparaginase per cycle) have been shown to be effective for the treatment of ENKL.[48-50]

In a phase II study from the NK-Cell Tumor Study Group (38 patients with newly diagnosed stage IV, and relapsed or refractory ENKL, nasal type), the SMILE regimen resulted in an ORR of 79% (45% CR).[48] The response rates were not different between patients with newly diagnosed stage IV and those with relapsed or refractory disease. The 1-year PFS and OS rates were 53% and 55%, respectively. 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.[49] The ORR was 81% (66% CR), and similar response rates were observed between patients with newly diagnosed and relapsed/refractory disease. At a median follow-up of 31 months, the 4-year DFS and OS rates were 64% and 50%, respectively.

In a retrospective analysis of 43 patients with ENKL, nasal type treated at a single institution (26 patients with early-stage disease received 2 cycles of chemotherapy followed by 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 with advanced-stage disease (*P* < .001) for the total cohort of patients.[50]

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.[51-53] 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.[51] 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 with relapsed/refractory disease, but there were no differences in OS.

The DDGP (dexamethasone, cisplatin, gemcitabine, and pegaspargase) regimen is an effective treatment option with a better toxicity profile in patients with newly diagnosed as well as relapsed/refractory ENKL.[54,55] In a prospective, multicenter, randomized trial (87 eligible patients with newly diagnosed ENKL; 80 patients included in the intent-to-treat population were randomized to receive the DDGP or SMILE regimen), the DDGP regimen was better tolerated and was also associated with significant improvement in PFS and OS compared with the SMILE regimen.[54] At median follow-up of 42 months, the median PFS and OS were not reached in patients treated with the DDGP regimen. The median PFS and OS were 7 months and 75 months, respectively, for patients treated with the SMILE regimen. The DDGP regimen was also associated with higher ORR (90% vs. 60%; *P* = .002), 3-year PFS rate (57% vs. 42%; *P* = .004), and 5-year OS rate (74% vs. 52%; *P* = .02), although there was no difference in CR rate between the two groups. The incidences of non-hematologic toxicities (eg, elevated transaminase, mucositis, allergy) and grade 3 or 4 hematologic toxicities were higher with the SMILE regimen than with DDGP. However, the dosing and supportive care used for the SMILE regimen on this study differed from those used for the conventional SMILE or modified SMILE regimen, which may have contributed to this difference.

The AspaMetDex regimen (L-asparaginase, methotrexate and dexamethasone) was evaluated in a phase II intergroup study in 19 patients with refractory or relapsed ENKL.[56] After three 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 three 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 clearance of serum EBV-DNA were significantly associated with a better outcome.[56]

Combined Modality Therapy

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%).[3] In the subgroup of patients with early-stage ENKL, nasal type (n = 57), combined modality therapy resulted in significantly improved 3-year OS rate compared to chemotherapy alone (57% vs. 30%; *P* = .045).[3]

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.[37] Notably, in this study, the addition of chemotherapy to RT did not appear to improve OS outcomes. 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).

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, and the survival benefit was seen in patients who achieved CR after chemotherapy.[57-60] In a study of 240 patients with early-stage ENKL treated with asparaginase-based chemotherapy with or without RT, the use of RT in combination with chemotherapy was associated with significantly improved 5-year OS rates (85% vs. 59%; *P* = .006), DFS rates (76% vs. 44%; *P* = .001), and locoregional control (85% vs. 62%; *P* = .026).[58] The omission of RT was associated with poor prognosis and resulted in frequent locoregional recurrence even in patients who achieved a CR after asparaginase-based chemotherapy. The 5-year cumulative disease recurrence rate was significantly higher for patients treated with chemotherapy alone (47% vs.19%; *P* = .003).

The use of IMRT in combination with chemotherapy results in promising clinical outcomes in patients with early-stage ENKL, with mild toxicities related to RT.[61-63]

Concurrent Chemoradiation

Concurrent chemoradiation therapy (CCRT; 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), patients with high-risk, 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]).[64] 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.[65] 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 retrospective analysis (358 patients; 257 patients had localized disease) also reported favorable response and survival rates for patients treated with the CCRT with DeVIC regimen.[66] After a median follow-up of 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 a multivariate analysis, elevated soluble interleukin-2 receptor was an independent predictive factor for worse OS and PFS among patients treated with CCRT with the DeVIC regimen.

Another phase II study also reported promising results with CCRT with 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).[67] 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.[67] The safety and efficacy of CCRT followed by consolidation chemotherapy in patients with localized ENKL, nasal type has also been confirmed in other studies.[68,69]

Sequential Chemoradiation

Chemotherapy followed by RT also resulted in significantly higher response rates and prolonged survival in patients with advanced-stage disease.[40] 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).[40] 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 did not provide a significant survival advantage among those with stable or progressive disease after initial chemotherapy.[40]

In the aforementioned retrospective analysis that evaluated the modified SMILE regimen in patients with ENKL, among the 11 patients with early-stage disease treated with sequential chemoradiation (2 cycles of the modified SMILE regimen followed by ISRT), the estimated 2-year PFS rate was 83% and all patients were alive with no evidence of disease at the time of publication.[50]

Sequential chemoradiation with the modified SMILE regimen and low-dose IMRT resulted in long-term disease control in patients with early-stage ENKL, nasal type.[63] In a single-institution study of 28 patients with ENKL nasal type, the ORR at completion of the modified SMILE regimen was 93% (68% CR) and increased to 95% (88% CR) after the completion of sequential IMRT. At a median follow-up of 31 months, the PFS and OS rates were 92% and 100%, respectively, for patients with early-stage disease (low PINK-E). The corresponding PFS and OS rates were 33% and 43%, respectively, for patients with advanced-stage disease.

Sequential chemoradiation with P-GEMOX and DDGP regimens has also been associated with favorable efficacy and acceptable toxicity in patients with stage I–II ENKL. In a cohort of 202 patients with early-stage ENKL, sequential chemoradiation with P-GEMOX resulted in an ORR of 96% (83% CR) and the 3-year PFS and OS rates were 75% and 85%, respectively, with a median follow-up of 44 months.[53] DDGP followed by RT also resulted in higher ORR and longer PFS rates compared to RT alone or VIPD followed by RT in patients with stage I–II ENKL.[70,71] In a trial of 65 patients with stage I–II ENKL who were randomized to receive RT or DDGP followed by RT, the ORRs were higher for sequential chemoradiation with DDGP compared to RT (83% [73% CR] vs. 60% [49% CR]) and the 5-year PFS and OS rates were 83% and 86%, respectively, for sequential chemoradiation with DDGP.[70] The corresponding survival rates were 57% and 60%, respectively, for RT. In another trial of 40 patients with stage I–II ENKL, the ORR was higher for DDGP followed by RT (95%; 85% CR) compared to the VIPD followed by RT group (65%; 50% CR).[71] The 5-year PFS rates were 83% and 44%, respectively, for the two treatment groups (*P* = .005), although the 5-year OS rate was not significantly different between the two groups (83% vs. 72%; *P* = .631).

Sandwich Chemoradiation

Sandwich chemoradiation (2 cycles of chemotherapy followed by involved-field RT [IFRT] followed by 2–4 cycles of chemotherapy within 7 days of completion of IFRT) with the GELOX regimen (L-asparaginase, gemcitabine, and oxaliplatin) and P-GEMOX regimen is also effective for the treatment of newly diagnosed stage I–II ENKL, nasal type, resulting in an ORR of 96% (74% CR) and 92% (87% CR), respectively.[72,73] After a median follow-up of 63 months, the 5-year OS and PFS rates were 85% and 74%, respectively, for sandwich chemoradiation with the GELOX regimen.[72] After a median follow-up of 16 months, the 1-year PFS and OS rates were both 87% for sandwich chemoradiation with the P-GEMOX regimen.[73]

Sandwich chemoradiation with GELAD (gemcitabine, etoposide, pegaspargase, and dexamethasone) chemotherapy and IMRT was also effective for the treatment of early-stage ENKL, resulting in an ORR of 94% (92% CR).[74] After a median follow-up of 32 months, the estimated 4-year PFS and OS rates were 90% and 94%, respectively.

The results of another study showed that sandwich chemoradiation with the GELOX regimen and IMRT was associated with higher PFS rates (92% vs. 71%; *P* = .011) and a trend towards improved locoregional control (22% vs. 8%; *P* = .051) compared to sequential chemoradiation in

patients with early-stage ENKL.[61] The EBV-DNA copy number after treatment was a significant prognostic factor for locoregional recurrence, PFS, and OS.

Long-term benefit of this approach needs to be confirmed in larger prospective randomized clinical trials.

NCCN Recommendations

The optimal treatment approach has not yet been established for patients with ENKL. Because ENKL are rare malignancies, few randomized trials comparing different regimens have not been conducted to date. Most of the available data are from retrospective analyses and small prospective series. Participation in a clinical trial is the preferred option for all patients with ENKL. 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.

Combined modality therapy yields more favorable outcomes for patients with early-stage stage disease who are candidates for chemotherapy. In a retrospective analysis of 123 patients with ENKL treated at major North American academic centers, among the 83 patients with stage I/II disease, 53 patients (64%) were treated with combined modality therapy.[75] The outcomes were similar for patients who received combined modality therapy versus RT alone (2-year PFS rates were 53% vs. 47%; [*P* = .91] and the 2-year OS rates were 67% for each group).

Combined modality therapy is recommended for stage I or II ENKL, nasal type in patients who are fit to receive chemotherapy and also for those with stage IV ENKL, nasal type and ENKL, extranasal type (stage I–IV).

CCRT with DeVIC (3 cycles) and RT[65,66] or sequential chemoradiation (modified SMILE [2–4 cycles; 2 cycles for stage I–II disease] followed by RT) [50,63] or sandwich chemoradiation (2 cycles of P-GEMOX followed by RT followed by 2–4 cycles of P-GEMOX or 2 cycles of GELAD followed by RT followed by 2 cycles of GELAD)[73,74] are included as options for preferred regimens.

CCRT with cisplatin followed by VIPD chemotherapy (3 cycles) or sequential chemoradiation with DDGP (3–6 cycles; 3 cycles for stage I-II disease) followed by RT are included as options under other recommended regimens.[67,70,71]

RT alone is recommended for patients with stage I or II nasal disease who are unfit to receive chemotherapy. IFRT for solitary lesions can be considered in rare circumstances for stage IE primary cutaneous ENKL.

Combination chemotherapy (modified SMILE, P-GEMOX, or DDGP) with or without RT is also an option for patients with stage IV ENKL, nasal type and patients with ENKL, extranasal type (stage I–IV).[50,51,54] AspaMetDex is an option for selected patients who cannot tolerate more intensive chemotherapy.[56]

Response Assessment

Results from retrospective studies suggest that measurement of EBV-DNA and interim or post-treatment PET/CT scan using the Deauville 5-PS may be useful for the assessment of treatment efficacy and response assessment in patients with newly diagnosed and relapsed/refractory disease.[31-33,76-81]

Post-treatment EBV-DNA positivity (in whole blood or plasma) was a predictor of early relapse and poor prognosis for patients with early-stage ENKL treated with asparaginase- or pegaspargase-based chemotherapy.[31-33,76] A Deauville score of 4–5 on interim PET/CT scan and EBV DNA after completion of initial treatment have been independently associated with PFS and OS in the multivariable analysis.[78,81]

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. 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.

Additional Therapy

Observation (H&P, ENT evaluation, PET/CT scan, and measurement of EBV viral load by quantitative PCR) is recommended for all patients with stage I or II nasal disease achieving a CR or partial response (PR) (with negative biopsy) to induction therapy. A CR should also include a negative ENT evaluation.

Autologous HCT has been evaluated as a consolidation therapy for patients with ENKL responding to primary therapy.[82-87] In one retrospective analysis, among patients with CR at the time of transplant stratified by risk based on NK/T-cell prognostic index, the survival benefit with autologous HCT was significantly greater (100% vs. 52%) for patients in the high-risk group and 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%).[84] Other retrospective analyses have identified the NK/T-cell prognostic index for limited disease, pre-transplant response status assessed by the Deauville 5-point scale (5-PS), and the presence of detectable EBV-DNA as independent predictors of survival following autologous HCT.[85,86]

However, there are no clear data to suggest whether allogeneic or autologous HCT is preferred.[88] In a retrospective analysis from the Lymphoma Working Group of the Japan Society for Hematopoietic Cell Transplantation (JSHCT), that compared the outcomes following autologous HCT (n = 60) and allogeneic HCT (n = 74) in patients with ENKL, although the 2-year OS rate was significantly higher with autologous HCT compared with allogeneic HCT (69% vs. 41%), in multivariate analysis the type of transplant was not a significant prognostic factor.[88] Patients who underwent autologous HCT in this series appeared to have better prognostic features (greater proportion of patients had stage IV disease in the allogeneic HCT group compared to the autologous HCT group [64% vs. 33%], and the proportion of patients with low-risk IPI scores was also smaller in the allogeneic HCT group [34% vs. 62%]).

Consolidation with HCT should be considered for patients achieving a CR or PR (with negative biopsy) to induction therapy and treatment should be individualized.

Relapsed/Refractory Disease

Clinical trial is the preferred treatment option for relapsed/refractory disease following treatment with pegaspargase-based regimens.

Anti-programmed cell death protein 1 (PD-1) antibodies, pembrolizumab, and nivolumab have been shown to induce responses in patients with relapsed/refractory ENKL following treatment with asparaginase-based regimens.[89-91] In the absence of a clinical trial, pembrolizumab and nivolumab are included as preferred single-agent options for relapsed/refractory disease.

In a multicenter retrospective study of 135 patients with relapsed/refractory ENKL, the ORR was higher for those treated with asparaginase-based regimens (59%) than gemcitabine-based regimens (45%). Among patients treated with asparaginase-based regimens, the ORR were higher for those receiving the regimen for the first time for relapsed/refractory disease (74%) compared to 44% for those who had been previously treated with asparaginase-based chemotherapy.[92] Therefore, an alternate pegaspargase-based combination chemotherapy (not previously used for induction therapy) may offer benefit for patients with primary refractory disease or for those with PR (and positive biopsy) after induction therapy.[48,49,51,55]

The efficacy and safety of GDP (gemcitabine, dexamethasone, and cisplatin) in relapsed/refractory ENKL was described in a retrospective study (n = 41; 26 patients had relapsed/refractory disease).[93] The efficacy of brentuximab vedotin and pralatrexate in relapsed/refractory ENKL have been reported only in case reports.[94-96]

Brentuximab vedotin (BV) is approved for the treatment of mycosis fungoides/Sézary syndrome (MF/SS) and relapsed/refractory systemic anaplastic large cell lymphoma (ALCL) and it is also effective in other subtypes of CD30-positive PTCL. CD30 expression in ENKL is variable, with 38% to 56% of Asian patients having some positivity.[97,98] In clinical studies that have evaluated BV in patients with MF, responses were observed across all CD30 expression levels (including negligible CD30 expression).[99,100]

BV (for CD30-positive disease), pralatrexate, GDP, and other combination chemotherapy regimens (based on the extrapolation of their use for relapsed/refractory peripheral T-cell lymphoma [PTCL]) are included as alternative options (other recommended regimens). Romidepsin and belinostat may be useful under certain circumstances. Monitoring for EBV reactivation should be considered since severe EBV reactivation has been reported in patients with ENKL treated with histone deacetylase inhibitors.[101]

Allogeneic HCT been evaluated in retrospective studies and case reports predominantly in Asian patients.[83,102-109] The presence of a detectable level of EBV-DNA and disease status at the time of transplant were also predictive of outcome following allogeneic HCT (CR or PR before allogeneic HCT was associated with better survival outcomes than stable or progressive disease).[107] However, in a retrospective analysis from CIBMTR that evaluated allogeneic HCT in a predominantly white patient cohort, 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.[108] The results from a retrospective study based on a large cohort of non Asian patients with ENKTL showed that HCT provided survival benefit for patients with relapsed disease and high-risk clinical features who achieved second remission.[109]

These data suggest that consolidation with HCT should be considered in selected patients with relapsed ENKL. Allogeneic HCT is preferred, if a donor is available.

Aggressive NK-Cell Leukemia

Aggressive NK-cell leukemia (ANKL) is a rare form of large granular lymphocyte leukemia (LGLL), characterized by a systemic proliferation of NK cells, an aggressive clinical course and poor prognosis, and with a median survival of less than 2 months.[110] ANKL predominantly occurs in younger patients with a median age of 40 years. The most common signs and symptoms at presentation include fever, B-symptoms with concomitant hemophagocytosis, hepatosplenomegaly, and lymphadenopathy.[111] ANKL does not usually have nasal or skin

involvement and clinical EBV infection has been observed in a subset of patients. EBV-associated T- and NK-cell lymphoproliferative disorders (LPD), including chronic active EBV infection (CAEBV), can progress to ANKL.

EBV infection (detected by EBER-ISH) is present in the majority of cases with ANKL.[111] Similar to ENKL, measurement of EBV-DNA in peripheral blood by quantitative PCR is useful in the diagnosis and possibly in the monitoring of the disease. EBV-negative ANKL has also been reported, occurring mainly in older patients.[112,113]

ANKL cells consistently express CD2, cytoplasmic CD3 (epsilon chain), CD16, CD56, CD94, and cytotoxic molecules, such as granzyme B, TIA1, and perforin A.[111] Next-generation sequencing (NGS) studies have identified *TP53* mutations, mutations in epigenetic modifiers, as well as genetic mutations involved in the JAK/STAT and RAS-MAPK signaling pathways.[114-116]

The diagnosis of ANKL is most frequently confirmed by bone marrow biopsy. Adequate immunophenotyping is essential to confirm the diagnosis, especially to confirm the diagnosis of EBV-negative ANKL. The main differential diagnoses include NK-large granular lymphocytic leukemia (NK-LGLL; included as a definite entity in the 2022 WHO classification [WHO5]), CAEBV, EBV-positive T-cell and NK-cell lymphoproliferative diseases of childhood, ENKL, and rarely other EBV-associated T-cell lymphomas.

Treatment with anthracycline-based regimens is typically ineffective. An asparaginase-based or pegaspargase-based chemotherapy regimen (recommended for ENKL) can be used for the treatment of patients with ANKL.[117-120] However, there is no established chemotherapy regimen for the optimal treatment of ANKL. Allogeneic HCT may be helpful to improve the outcome of patients with ANKL and the panel favors consolidation with allogeneic HCT (over autologous HCT) for patients in first remission.[121]

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