National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Hodgkin's Lymphomas

Version 2.2015

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Peripheral T-Cell Lymphomas

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Peripheral T-Cell Lymphomas

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Discussion

DIAGNOSIS

ESSENTIAL:

- **Review of all slides with at least one paraffin block representative of the tumor should be done by a hematopathologist with expertise in the diagnosis of PTCL. Rebiopsy if consult material is nondiagnostic.**
- **An FNA alone is not sufficient for the initial diagnosis of peripheral T-cell lymphoma.**
- **Adequate immunophenotyping to establish diagnosis[a,b]**
  - **IHC panel: CD20, CD3, CD10, BCL6, Ki-67, CD5, CD30, CD2, CD4, CD8, CD7, CD56, CD57 CD21, CD23, EBER-ISH, ALK or**
  - **Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD3, CD5, CD19, CD10, CD20, CD30, CD4, CD8, CD7, CD2; TCRαβ; TCRγ**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **Molecular analysis to detect: antigen receptor gene rearrangements; t(2;5) and variants**
- **Additional immunohistochemical studies to establish lymphoma subtype: βF1, TCR-CγM1, CD279/PD1, CXCL-13**
- **Cytogenetics to establish clonality**
- **Assessment of HTLV-1[c] serology in at-risk populations. HTLV-1 PCR if serology is indeterminate.**

SUBTYPES

Subtypes included:

- **Peripheral T-cell lymphoma (PTCL), NOS**
- **Angioimmunoblastic T-cell lymphoma (AITL)[d]**
- **Anaplastic large cell lymphoma (ALCL), ALK positive**
- **ALCL, ALK negative**
- **Enteropathy-associated T-cell lymphoma (EATL)**

See Workup (TCEL-2)

Subtypes *not* included:

- **Primary cutaneous ALCL**
- **All other T-cell lymphomas**

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

[a] Molecular diagnosis for T-cell receptor rearrangements should be done in most circumstances to confirm clonality. T-cell receptor rearrangements alone are not sufficient for diagnosis, as these are often seen with reactive/inflammatory processes.

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

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

[d] AITL may occasionally present with concurrent DLBCL. EBV and appropriate immunohistochemistry should be performed.

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

WORKUP

ESSENTIAL:[e]

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

USEFUL IN SELECTED CASES:

- Neck CT
- Head CT or MRI
- Skin biopsy
- Discussion of fertility issues and sperm banking
- HIV testing

→ See Induction Therapy (TCEL-3)

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

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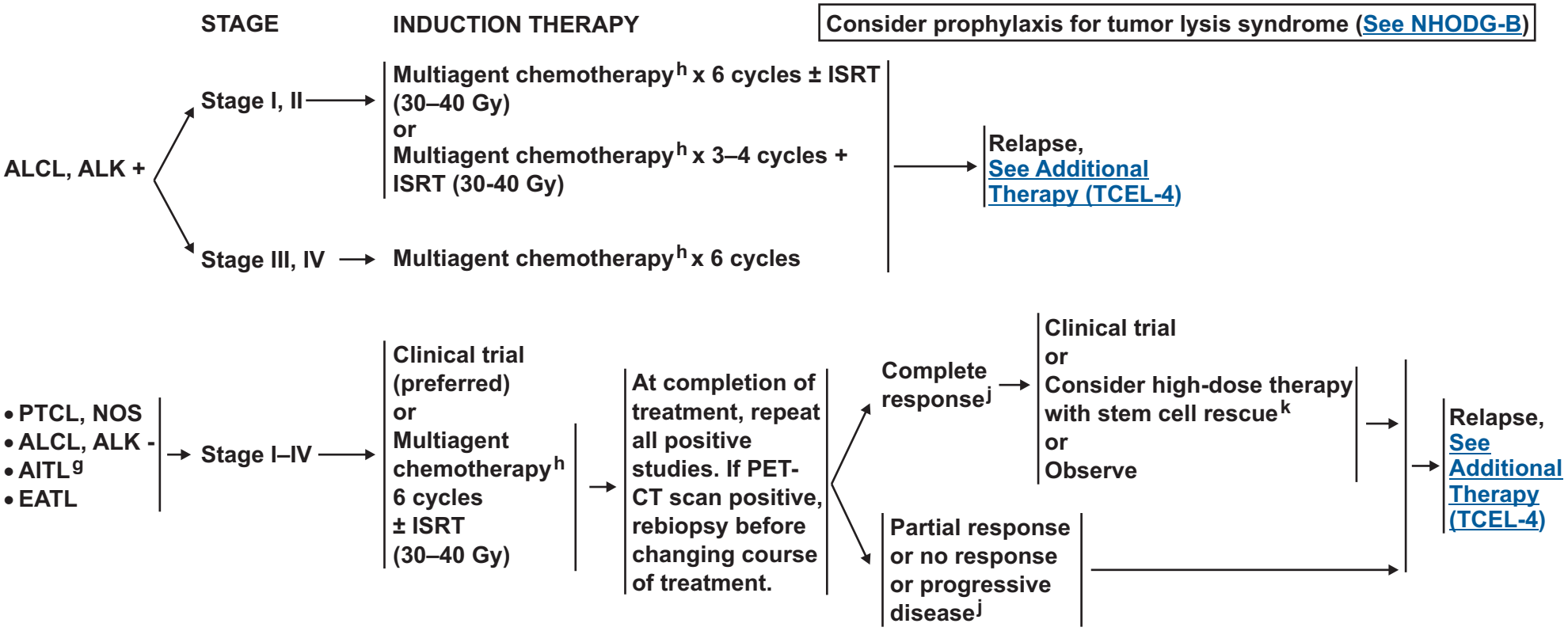

Breast implant-associated ALCL

- Emerging entity described as development of ALCL around the implant (involving the fibrous capsule and/or seroma only). In this setting, the natural history of this entity appears generally favorable with surgical removal of the implant alone as adequate therapy for most patients.
- However, rare cases with parenchymal breast or nodal involvement may have an aggressive course more in line with systemic ALCL ALK.
- Optimal treatment of these cases is not well defined and management should be individualized.

[g] For selected patients (elderly, comorbid conditions), a trial of single-agent corticosteroid may be considered for symptom management.

[h] See Suggested Treatment Regimens (TCEL-B).

[j] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).

[k] Localized areas can be irradiated before or after high-dose therapy.

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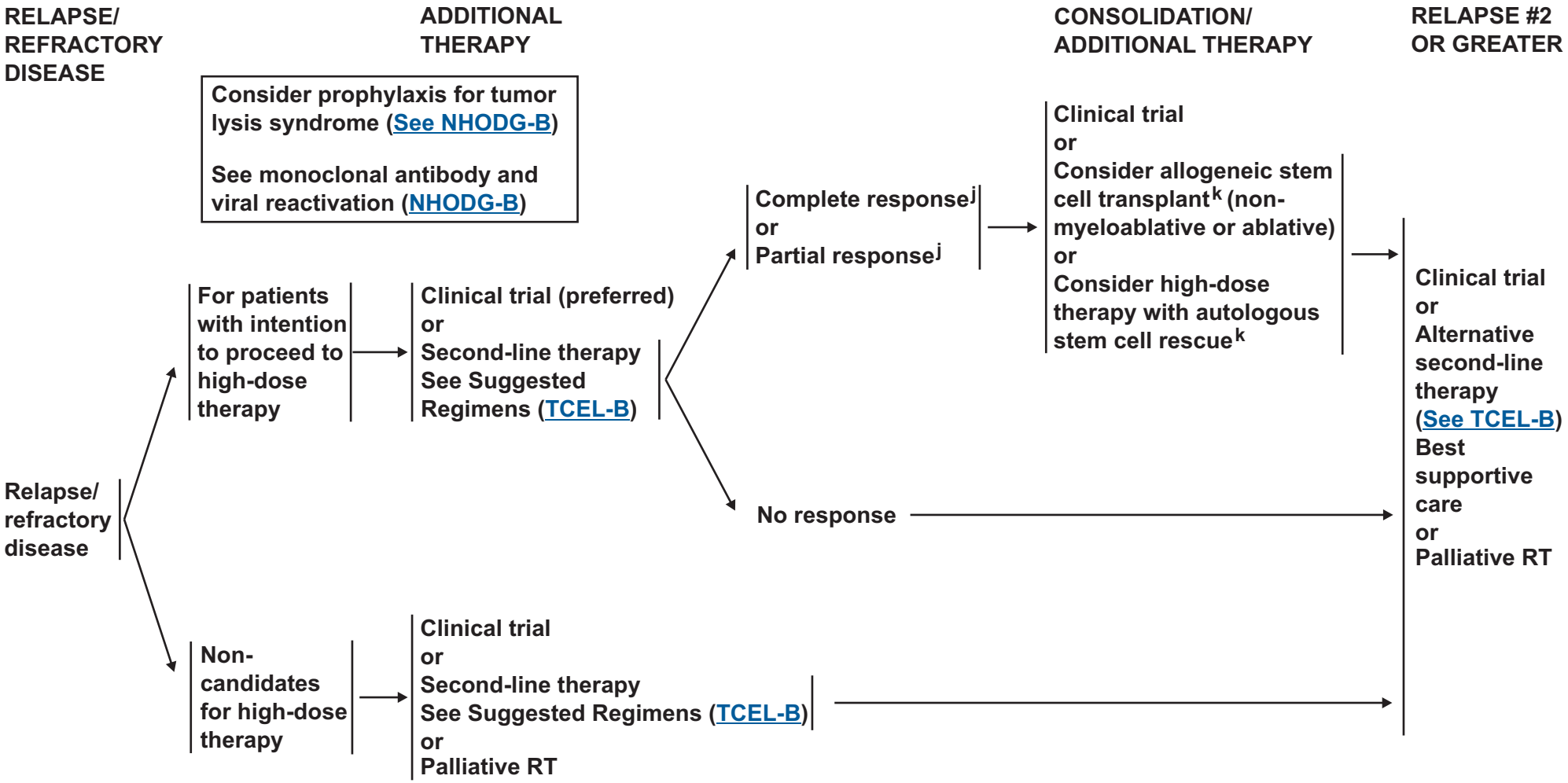

[j] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[k] Localized areas can be irradiated before or after high-dose therapy.

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INTERNATIONAL PROGNOSTIC INDEX[a]

ALL PATIENTS:
• Age >60 years
• Serum LDH > normal
• Performance status 2–4
• Stage III or IV
• Extranodal involvement >1 site

INTERNATIONAL INDEX, ALL PATIENTS:	
• Low	0 or 1
• Low intermediate	2
• High intermediate	3
• High	4 or 5

AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX[a]

PATIENTS ≤60 YEARS:
• Stage III or IV
• Serum LDH > normal
• Performance status 2–4

INTERNATIONAL INDEX, PATIENTS ≤60 YEARS:	
• Low	0
• Low/intermediate	1
• High/intermediate	2
• High	3

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

RISK FACTORS:
• Age >60 years
• Serum LDH > normal
• Performance status 2–4
• Bone marrow involvement

PROGNOSTIC RISK:	
• Group 1	0
• Group 2	1
• Group 3	2
• Group 4	3 or 4

[a] The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-hodgkin's lymphoma. N Engl J Med 1993;329:987-994.
[b] Gallamini A, Stelitano C, Calvi R, et al. Peripheral T-cell lymphoma unspecified (PTCL-U): A new prognostic model from a retrospective multicentric clinical study. Blood 2004;103:2474-2479.

Note: All recommendations are category 2A unless otherwise indicated.
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SUGGESTED TREATMENT REGIMENS[a]

First-line Therapy:

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

First-line Consolidation:

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

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

See Second-line and Subsequent Therapy on TCEL-B 2 of 3

[a] See references for regimens TCEL-B 3 of 3.

[b] While CHOP-21 and CHOEP-21 regimens confer a favorable prognosis in ALCL, ALK +, these regimens have not provided the same favorable results for other PTCL histologies; clinical trial is therefore preferred for the management of these other histologies.

[c] CHOP followed by IVE regimen includes HSCT.

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SUGGESTED TREATMENT REGIMENS[a]
(in alphabetical order)

Second-line and Subsequent Therapy (intention to proceed to high-dose therapy):

- Clinical trial preferred
- Bendamustine
- Belinostat (category 2B)
- Brentuximab vedotin for systemic ALCL excluding primary cutaneous ALCL
- Brentuximab vedotin for systemic CD30+ PTCL
- DHAP (dexamethasone, cisplatin, cytarabine)
- ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)
- Dose-adjusted EPOCH
- GDP (gemcitabine, dexamethasone, cisplatin)
- GemOx (gemcitabine, oxaliplatin)
- ICE (ifosfamide, carboplatin, etoposide)
- Pralatrexate[d]
- Romidepsin

Second-line and Subsequent Therapy (non-candidate for high-dose therapy):

- Clinical trial preferred
- Alemtuzumab
- Bendamustine
- Belinostat (category 2B)
- Bortezomib[e] (category 2B)
- Brentuximab vedotin for systemic ALCL excluding primary cutaneous ALCL
- Brentuximab vedotin for systemic CD30+ PTCL
- Cyclosporine for AITL only[f]
- Dose-adjusted EPOCH
- Gemcitabine
- Pralatrexate[d]
- Radiation therapy
- Romidepsin

See First-line Therapy on TCEL-B 1 of 3.

[a] See references for regimens TCEL-B 3 of 3.
[d] In AITL, pralatrexate has limited activity.
[e] Activity has been demonstrated in small clinical trials and additional larger trials are needed.
[f] With close follow-up of renal function.

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

SUGGESTED TREATMENT REGIMENS
References

First-line Therapy

CHOP

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

CHOP or CHOP-14 with or without etoposide

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

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

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

CHOP followed by IVE

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

Dose-adjusted EPOCH

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

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

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

HyperCVAD alternating with high-dose methotrexate and cytarabine

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

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

Second-line Therapy

Alemtuzumab

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

Belinostat

O'Connor O, Masszi T, Savage K, et al. Belinostat, a novel pan-histone deacetylase inhibitor (HDACi), in relapsed or refractory peripheral T-cell lymphoma (R/R PTCL): Results from the BELIEF trial [abstract]. J Clin Oncol 2013;31:Abstact 8507.

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.

Brentuximab vedotin

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

Jacobsen ED, Advani RH, Oki Y, et al. A Phase 2 Study of Brentuximab Vedotin in Patients with Relapsed or Refractory CD30-Positive Non-Hodgkin Lymphomas: Interim Results [abstract]. Blood 2012;120: Abstract 2746.

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

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

Cyclosporine for AITL

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

DHAP (dexamethasone, cisplatin, cytarabine)

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

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

ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)

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

Gemcitabine

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

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

GDP (gemcitabine, dexamethasone, cisplatin)

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

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

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

GemOX (gemcitabine, oxaliplatin)

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

ICE (ifosfamide, carboplatin, etoposide)

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

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.

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Peripheral T-Cell Lymphomas

Peripheral T-cell lymphomas (PTCL) are a heterogeneous group of lymphoproliferative disorder arising from mature T-cells of post-thymic origin.[1] PTCL represent a relatively uncommon group of hematologic malignancies within non-Hodgkin lymphomas (NHL), accounting for about 10% of NHL cases.[2] The prognosis for PTCL remains poor in comparison to B-cell NHL. This is largely due to lower response rates and less durable responses to standard combination chemotherapy regimens such as CHOP. Progress has been further hampered by the relative rarity and the biological heterogeneity of the diseases. Among PTCL cases worldwide, the most common subtypes include PTCL-not otherwise specified (PTCL-NOS; 26%), angioimmunoblastic T-cell lymphoma (AITL; 18.5%), NK/T-cell lymphoma (10%), adult T-cell leukemia/lymphoma (ATLL; 10%), ALK-positive anaplastic large cell lymphoma (ALCL; 7%) and ALK-negative ALCL (6%); subtypes such as enteropathy-associated T-cell lymphoma (EATL; <5%) and primary cutaneous ALCL are relatively rare (<2%) with ALCL more common than NK/T or ATLL in the United States.[3]

PTCL-NOS is the most common subtype of PTCL. It most often involves nodal sites, however, many patients present with extranodal involvement including the liver, bone marrow, GI tract and skin. PTCL-NOS is associated with poorer overall survival (OS) and event-free survival (EFS) rates compared to B-cell lymphomas.[4-6]

AITL usually presents with generalized lymphadenopathy, often with associated hepatomegaly or splenomegaly, hypergammaglobulinemia, eosinophilia, skin rash and fever. It occurs mainly in older patients. Prognosis is similar to PTCL-NOS. In a single institution study, which reviewed the data from 199 patients with PTCLs, the 5-year OS and PFS rates were 36% and 13%, respectively, for the subgroup of patients with AITL.[6] In the most recent report from the GELA study, which included the largest series of patients with AITL (n=157), 5- and 7-year OS rates were 33% and 29%, respectively, reaching an apparent plateau around 6 years.[7] The corresponding EFS rates were 29% and 23%, respectively.

ALCL is a CD30-expressing subtype of PTCL which accounts for less than 5% of all cases of NHL. There are now three distinctly recognized subtypes of ALCL: systemic ALK-1 expressing ALCL, systemic ALK-1 negative ALCL, and primary cutaneous ALCL. ALK-positive ALCL is most common in children and young adults. It is characterized by the overexpression of anaplastic lymphoma kinase (ALK-1) protein, which is the result of a chromosomal translocation [t(2;5)] in 40-60% of patients.[8] Systemic ALK-positive ALCL predominantly occurs at younger age and has a good prognosis compared to ALK-negative ALCL, which occurs in older patients. The majority of patients with ALCL present with advanced stage III or IV disease (65% for ALK-positive and 58% for ALK-negative) frequently associated with systemic symptoms and extra nodal involvement.[3] In general ALK-positive ALCL is associated with better clinical outcomes than ALK-negative ALCL, PTCL-NOS or AITL although the favorable prognosis of ALK-1 positivity is diminished with older age and higher prognostic risk scores. Five-year OS rate following anthracycline-based therapy was 79% for ALK-positive ALCL compared to 46% for ALK-negative ALCL.[9] Recent survival analysis from the International T-cell Lymphoma Project also reported similar outcomes.[3,10] The differences in prognosis are most pronounced for younger patients with favorable prognostic factors. In this report, ALK-positive ALCL was associated with significantly better prognosis with anthracycline-containing regimens compared with ALK-negative ALCL, both in terms of the 5-year failure-free survival (FFS) rate (60% vs. 36%; *P*=0.015) and OS rate (70% vs. 49%; *P*=0.016).[10] The 5-year FFS

and OS rates for patients with PTCL-NOS were 20% and 32%, respectively. The 5-year FFS and OS rates for patients with AITL were 18% and 32%, respectively.[3]

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

During the last decade, numerous reports of primary breast ALCL occurring in association with breast implants have appeared in anecdotal reports and case series. NHL of the breast is rare, comprising only <0.5% of malignant breast tumors and about 2% of extranodal lymphomas.[11-13] The majority of cases of NHL of the breast are of B-cell origin.[11-15] However, in recent years, reports have emerged that suggest an association between breast implants and ALCL of the breast.[11,12,16] In a matched case-control study based on a national pathology registry from the Netherlands, 11 patients with ALCL of the breast were identified over a 17-year time period; pathological and clinical characteristics of these patients were compared with those of control patients (n=30; matched for age and year of diagnosis) with other types of lymphomas in the breast.[16] Five of the patients with breast ALCL had received breast implants while one patient in the control group had received an implant prior to lymphoma diagnosis. The odds ratio for ALCL associated with breast implants was 18 (95% CI, 2-157).[16] Thus, the probability of developing ALCL was higher among women with breast implants compared with those without implants, although the absolute risk remains very low given the rarity of ALCL of the breast.

ALCL associated with breast implants are frequently ALK-negative, and primarily occur within the fibrous capsule around the implant, within the periimplant fluid, as a seroma, or otherwise within the vicinity of the implant.[11,12,16,17] Based on a literature review of the clinical and histological findings of ALK-negative ALCL associated with breast implants, it has been suggested that this lymphoma may represent a distinct entity from systemic ALCL, but may be more similar to primary cutaneous or indolent ALCL in terms of clinical behavior.[11,12] Although the majority of reported cases of ALCL associated with breast implants appear to be limited to localized disease, systemic involvement and death due to ALCL have also been rarely reported.[11,18] These reported cases of aggressive disease appear more common in ALCL of the breast parenchyma rather than of the fibrous capsule or seroma and may represent a different process than has been reported in the majority of the implant associated cases. At the present time it is unclear as to the best management strategy for implant associated ALCL localized to the capsule or seroma. For patients with localized disease it appears that removal of the implant and the capsule are sufficient for many but predictors to identify the infrequent patients with a higher risk for dissemination are not known.[11,17,18]

Given the concern raised by the medical community with regards to breast implants and its putative association with ALK-negative ALCL, the FDA recently conducted a literature-based assessment to better characterize the potential association between implants and ALCL. In the report, the FDA indicated that "women with breast implants may have a very small but increased risk of developing this disease in the scar capsule adjacent to the implant" but that "the totality of evidence continues to support a reasonable assurance that FDA-approved breast implants are safe and effective when used as labeled".[19] At this time,

the pathogenesis of ALCL associated with breast implants and the causal effect of such implants remain unknown.

EATL is a rare T-cell lymphoma of the small intestine, accounting for <1% of all the NHLs and associated with a very poor prognosis. The median age of diagnosis is 60 years. The typical immunophenotype of EATL is CD3+, CD5–, CD7+, CD8–/+, CD4– and CD103+. Anthracycline-based chemotherapy with CHOP or CHOP-like regimens is most commonly used for patients with EATL[20-23]; however, outcomes remain poor with these conventional therapeutic approaches. In the aforementioned analysis from the International T-cell Lymphoma Project, the 5-year FFS and OS rates in patients with EATL primarily treated with anthracycline-based regimens were 4% and 20%, respectively.[3] Recent studies have shown that more intensive regimens followed by high-dose therapy followed by autologous stem cell rescue (HDT/ASCR) may improve outcomes in patients with EATL.[24-26]

Staging and Prognosis

Staging is similar to that of the other aggressive lymphomas. Historically, the International Prognostic Index (IPI) derived for DLBCLs has been used and was shown to have prognostic value for patients with PTCL. In 2004, the Italian Intergroup for lymphoma proposed a new prognostic index for PTCL-NOS.[4] Risk factors identified based on multivariate analysis included the following: age older than 60 years, elevated LDH levels, performance status of 2 or more, and bone marrow involvement. Five-year OS rate was only 33% for patients with 2 risk factors and 18% for those with 3 or 4 risk factors. This schema also identified a subset of patients with relatively favorable prognosis, who had adverse risk factors.[4] This group represented 20% of patients and had a 5-year OS rate of 62%. In the NCCN Guidelines, patients with stage I-II disease are stratified into 2 groups (low intermediate risk and high intermediate risk) based on the age-adjusted International Prognostic Index (aaIPI).

In a retrospective GELA study, the prognosis of patients with PTCL (including all subgroups) were compared with patients with B-cell lymphoma with similar characteristics receiving similar aggressive combination chemotherapy, and in some patients, receiving HDT/ASCR.[5] The CR rates were 63% and 54% for patients with B-cell lymphoma and PTCL, respectively. The 5-year event-free survival (EFS) rates were 45% and 32%, respectively. The 5-year OS rate was also higher for patients with B-cell lymphomas compared with patients with PTCL (52% vs. 41%). The difference in 5-year OS rates between B-cell lymphomas and PTCL were most pronounced in patients with 2 or 3 adverse risk factors as determined by IPI (53% vs. 36% for 2 risk factors; and 35% vs. 23% for 3 risk factors).[5] Initial characteristics and prognostic features were analyzed in another retrospective study in 174 patients with PTCL. Most patients were treated with anthracycline-based regimens.[27] The complete response (CR) rates (69% vs. 45%) and median survival (65 months vs. 20 months) were better for ALCL subgroup compared to other PTCL subtypes.

Diagnosis

Diagnosis of PTCL is similar to that described for other lymphomas, requiring adequate immunophenotyping to distinguish PTCL from B-cell neoplasms. The initial paraffin panel for immunohistochemistry (IHC) studies may only include pan-T-cell markers and can be expanded to include antibodies of T-cell lymphoma, if suspected. The following markers should be considered for the IHC analysis: CD2, CD3, CD5, CD7, CD4, CD8, CD30, CD56, CD57, CD10, CD20, CD21, CD23, ALK, EBER-ISH, BCL6, and Ki-67. Alternatively, the following markers can be analyzed by flow cytometry: CD2, CD3, CD5, CD7, CD4, CD8, CD30,

CD10, CD19, CD20, CD45, kappa/lambda, TCRαβ, and TCRγ. Additional IHC studies to evaluate βF1, CD279/PD1, and CXCL-13 may be useful under certain cases to establish lymphoma subtype. PTCL is often associated with clonal rearrangements of the T-cell receptor (TCR) genes that are less frequently seen in non-cancer T-cell diseases, although false positive results or non-malignant clones can at times be identified. Under certain circumstances, molecular analysis to detect *TCR* gene rearrangements and translocations involving the *ALK* gene, i.e., t(2;5) or variant, may be useful.

PTCL-NOS has variable T-cell associated antigens and usually lacks B-cell associated antigens (although aberrant CD20 expression in T-cell lymphomas is infrequently encountered). With the exception of CD30 expression in ALCL, antigen expression is variable across the aggressive T-cell lymphomas. The majority of the nodal cases express CD4+ and lack CD8-, however CD4-/CD8+, CD4-/CD8-, and CD4+/CD8+ cases are seen.[28] While CD30 expression can be found at times in many T-cell lymphomas, systemic ALCL has uniform strong expression of CD30. In ALCL cases only, evaluation of ALK1 status, either based on immunophenotyping or genetic analysis of the t(2;5) or variant chromosomal rearrangements, is important to identify the ALK1 positive tumors that have a better prognosis. AITL cells express T-cell associated antigens and are usually CD4+. Expression of CXCL13 has been identified as a useful marker that may help distinguish AITL from PTCL-NOS.[29,30] It is also characterized by the frequent presence of Epstein-Barr virus (EBV)-positive B-cells and cases of co-existent EBV+DLBCL are reported. EBER (EBV-encoded RNA) is positive in about 40% of PTCL and some case series have reported that EBER positive tumors have a worse prognosis.

Workup

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

Treatment Options

Induction Therapy

PTCLs are less responsive to and have less frequent durable remissions with standard chemotherapy regimens such as CHOP and thus carry a poorer prognosis compared to diffuse large B-cell lymphomas. In prospective randomized studies, PTCLs have been included with aggressive B-cell lymphomas.[31,32] However, it has not been possible to assess the impact of chemotherapy in this subgroup of patients with PTCLs due to small sample size. Only limited data exist from randomized trials comparing the efficacy of chemotherapy regimens exclusively in patients with PTCL.[33]

CHOP chemotherapy is the most commonly used first-line regimen for patients with PTCL. However, with the exception of ALK+ ALCL,

outcomes are disappointing compared to the favorable results achieved with DLBCL. Chemotherapy regimens that are more intensive than CHOP have not shown any significant improvement in OS in patients with PTCL, with the exception of ALCL.[34,35]

CHOP chemotherapy is frequently curative in only the small number of patients with favorable prognostic features.[3,10] As previously discussed, retrospective analysis from the International T-cell Lymphoma Project showed that anthracycline-based chemotherapy did not favorably impact survival in patients with the most common forms of PTCLs, namely PTCL-NOS and AITL.[3] In a retrospective study conducted by the British Columbia cancer agency, the 5-year OS rate for patients with PTCL-NOS primarily treated with CHOP or CHOP-like regimens was only 35%; among these patients, the 5-year OS rates were higher in patients with low-risk IPI scores compared with those with high-risk IPI scores (64% vs. 22%, respectively).[6] In addition, patients with ALK-positive ALCL had superior clinical outcome compared to those with ALK-negative ALCL (5-year OS 58% vs. 34%, respectively). The addition of etoposide to CHOP (CHOEP regimen) compared with CHOP alone was evaluated in a randomized study by the German High-grade NHL Study Group (DSHNHL). In relatively young patients with favorable prognosis aggressive NHL (age ≤60 years; normal LDH levels), the CHOEP regimen resulted in significantly higher CR rate (88% vs. 79%; *P*=0.003) and 5-year EFS rate (69% vs. 58%; *P*=0.004).[36] No difference was observed in OS outcomes between the regimens. It should also be noted that in this study, the majority of patients had B-cell histology, with only 14% diagnosed with T-cell NHL (with 12% of patients having ALCL, PTCL-NOS, or AITL histology).[36] In an analysis of a large cohort of patients with PTCL treated within the DSHNHL trials, patients with ALK-positive ALCL had favorable outcomes with CHOP or CHOP with etoposide (CHOEP).[35] Three-year EFS and OS rates were 76% and 90%, respectively, for patients with ALK-positive ALCL. The corresponding outcomes were 50% and 67.5%, respectively, for AITL, 46% and 62%, respectively, for ALK-negative ALCL and 41% and 54%, respectively, for PTCL-NOS. Among those with T-cell lymphoma, CHOEP was associated with a trend for improved EFS among relatively young patients (age <60 years) and is an option for these patients. CHOP-21 appeared to be the standard regimen for patients age >60 years, given that the addition of etoposide did not provide an advantage in these older patients due to increased toxicity. Among patients with ALK-negative ALCL, AITL and PTCL-NOS, those with low-risk IPI scores (IPI <1) had a relatively favorable prognosis; contrastingly, patients with higher risk IPI scores derived minimal benefit from CHOP or CHOEP.[35]

Intensive chemotherapy regimens have also been evaluated in the treatment of patients with PTCL. In a retrospective analysis of data from patients with T-cell malignancies treated at the MD Anderson Cancer Center (N=135; PTCL-NOS, n=50; ALCL, n=40; AITL, n=14), outcome with CHOP was compared with outcomes with more intensive chemotherapy regimens, one of which included a regimen with hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and prednisone (hyper-CVAD).[34] The estimated median OS was 46 months for all patients. The 3-year OS rate with CHOP and intensive therapies was 62% and 56%, respectively. Within the subgroup of patients with ALCL, those with ALK-positive disease showed a trend for a higher 3-year OS rate compared with those with ALK-negative ALCL (100% vs. 70%, respectively).[34] When the subgroup with ALCL was excluded from the analysis, the median OS was 21 months; the 3-year OS rate with CHOP and intensive therapies was 43% and 49%, respectively.[34] A combination chemotherapy regimen with etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (EPOCH) was first

evaluated by NCI investigators in patients with relapsed/refractory NHL,[37] and this regimen was recently evaluated in patients with previously untreated disease. In a prospective study that evaluated dose-adjusted EPOCH in previously untreated patients with PTCL (N=38; ALK-positive ALCL, n=15; ALK-negative ALCL, n=7; other PTCL, n=16), similar outcomes were reported for ALK-positive and ALK-negative ALCL.[38] The 5-year PFS rates in these subgroups were 80% and 71%, respectively; the 5-year OS was 86% in both groups. Outcomes for non-ALCL subtypes (PTCL-NOS, n=10; AITL, n=1; EATL, n=1; other, n=4) were poorer, with a 5-year PFS and OS of only 32% and 50%, respectively.[38] These results are encouraging for patients with ALCL, but outcomes with chemotherapy regimens remain suboptimal for those with non-ALCL subtypes.

The generally poor results with conventional chemotherapy have led many to explore the role of HDT/ASCR as a first-line consolidation therapy option. Several retrospective studies[39-47] have reported positive outcomes with HDT/ASCR in patients with PTCL. The 3-year OS rate in retrospective studies ranged from 53% to 58% in patients undergoing HDT/ASCT during first-line or subsequent lines of therapy; the 3-year PFS rate correlated with OS outcomes, and ranged from 44% to 50%.[39,47,48] Patients with the AITL subtype generally have poor outcomes, and HDT/ASCR may offer a feasible option for these patients, particularly in the setting of first remission.[42,45,49] In an analysis of data from a large cohort of patients with AITL from the EBMT Lymphoma Registry (N=146), the 2-year and 4-year OS rates overall for patients undergoing HDT/ASCR were 67% and 59%, respectively.[42] For the subgroup of patients who underwent HDT/ASCR in first CR, the 2-year and 4-year OS rates were 81% and 78%, respectively. These data point to the potential promising role of HDT/ASCR for patients with AITL in first CR.

Prospective studies have also demonstrated the potential role of HDT/ASCR in improving treatment outcome in patients with PTCL.[25,50-55] The Nordic lymphoma group evaluated dose-dense induction therapy with CHOEP followed by HDT/ASCR in patients with previously untreated PTCL responding to initial induction (NLG-T-01 study).[25,54,56] Patients with ALK-positive ALCL were excluded from this study. Among 160 patients enrolled with histopathologically confirmed PTCL (PTCL-NOS, 39%; ALK-negative ALCL, 19%; AITL, 19%; EATL, 13%), 115 patients (72%) underwent HDT/ASCR.[25] With a median followup of 60.5 months, the 5-year OS and PFS rates were 51% and 44%, respectively. Treatment-related mortality (TRM) was 4%. The 5-year OS and PFS for the subgroup of patients with PTCL-NOS was 47% and 38%, respectively. Among the subgroup of patients with ALK-negative ALCL, the corresponding rates were 70% and 61%, respectively.[25] In the prospective study conducted by the GELTAMO Study group (N=26), patients with CR or PR to induction therapy with MegaCHOP were planned for ASCR.[50] The 3-year OS and PFS rates on an intent-to-treat basis were 73% and 53%, respectively. At 2-year post-transplant follow-up, OS and PFS rates were 84%and 56%,respectively, among the patients who proceeded to ASCR consolidation (n=19).[50] In a phase II study (N=41), newly diagnosed patients with PTCL responding to high-dose CHOP regimen alternating with etoposide, cisplatin, cytarabine and prednisone, were planned for ASCR.[52] With a median follow-up of 3.2 years, the 4-year OS and PFS rates were 39% and 30%, respectively.

Reimer et al reported the final analysis of the first prospective PTCL-restricted multicenter study on upfront HDT/ASCR in 83 patients.[53] The treatment regimen consisted of four to six cycles of CHOP followed by HDT/ASCR. The ORR following CHOP chemotherapy was 79% (39% CR). Fifty-five of the 83 patients (66%)

received transplantation; the remaining 34% of patients were unable to proceed to transplant, primarily due to progressive disease. After HDT/ASCR, 48 of the 55 patients achieved a CR, and 7 patients achieved a PR. In an intent-to-treat analysis, the ORR after myeloablative therapy was 66% (56% CR). The estimated 3-year OS and PFS rates were 48% and 36%, respectively.[53]. Aggressive chemotherapy with CHOP followed by IVE/MTX (ifosfamide, etoposide and epirubicin alternating with intermediate-dose methotrexate) and HDT/ASCR has been evaluated as initial therapy with positive outcomes in patients with PTCL (N=57).[55] Among these patients, 33 proceeded to ASCR. Based on intent-to-treat analysis, the 3-year OS and PFS rates were 67% and 59%, respectively, for all patients.[55] An ongoing international randomized phase III trial is evaluating the role of adding the CD52 monoclonal antibody alemtuzumab (studies with alemtuzumab are discussed below under relapsed/refractory disease) to CHOP induction (versus CHOP alone; standard arm) in patients with previously untreated PTCL (ACT trial).[57] Patients with ALCL were excluded regardless of ALK status. Patients age 60 years or younger were eligible to proceed with HDT/ASCR (ACT-1). Results from the planned interim analysis of the younger ACT-1 patient group (n=68) reported 1-year EFS of 55%. The 1-year OS and PFS rates were 78% and 54%, respectively. Viral infectious events were more frequent in the alemtuzumab arm (28% vs. 10%), primarily due to asymptomatic cytomegalovirus (CMV) reactivations. The frequency of grade 3 or higher bacterial and fungal infections were similar between treatment arms.[57]

The outcome of ALK-positive ALCL patients undergoing ASCR compared to those with other histological subtype of PTCL was reported in only one prospective study by Corradini et al.[51] The pooled results from two prospective studies (N=62) showed that at a median follow-up of 76 months, the estimated 12-year OS and EFS rates were 34 and 30%, respectively, for the whole study cohort. Overall treatment-related mortality rate was 5%. The 10-year OS and EFS rates were significantly higher among the patients with ALK-positive ALCL (63% and 54%, respectively) compared with patients with other PTCL subtypes (21% and 19%, respectively). In the subgroup of patients with PTCL-NOS, the corresponding survival rates were 37% and 25%, respectively.[51] In a multivariate analysis, the achievement of CR before transplant was a strong predictor of survival benefit. The projected 10-year OS and EFS rates for patients in CR before transplant were 48% and 47%, respectively, compared with 22% and 11%, respectively, for those who were not in CR prior to transplant.[51]

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

NCCN Recommendations

For patients with ALK-positive ALCL, multiagent chemotherapy (typically CHOP-21 or CHOEP-21) for 6 cycles with or without radiation therapy (RT; an option for stage I-IV disease) or for 3 to 4 cycles with RT (an option in patients with stage I-II disease) is considered standard first-line therapy. Although CHOP or CHOEP regimens are associated with a favorable prognosis in patients with ALK-positive ALCL, these regimens have not resulted in similarly favorable outcomes for patients with other PTCL histologies. Thus, for patients with other subtypes, participation in clinical trials is the preferred management approach. In the absence of suitable clinical trials, multiagent chemotherapy (4-6 cycles) with adjuvant locoregional RT to involved region is

recommended for patients with stage I-II disease (low/low-intermediate risk); patients with higher risk stage I-II (high/high-intermediate risk) or stage III-IV disease are treated with multiagent chemotherapy (6-8 cycles) with or without RT. Suggested multiagent chemotherapy regimens include CHOEP, CHOP-14, CHOP-21, CHOP followed by ICE or IVE, dose-adjusted EPOCH, or hyper-CVAD.

AITL is a highly heterogeneous disease and can at times be treated solely with corticosteroids or other immunosuppressive agents. Cyclosporine has been effective in patients with relapsed disease following treatment with steroid or multiagent chemotherapy.[58] These milder or alternate approaches are often most appropriate for the elderly or those felt to be unlikely to tolerate a combination chemotherapy approach. Most patients with AITL are managed similarly to other forms of PTCL as above; however the NCCN Guidelines panel suggests a trial of singe-agent corticosteroid for symptom management in elderly patients or in patients with comorbid conditions in whom the risks of combination chemotherapy are excessive.

Breast implant-associated ALCL is an emerging clinical entity with unknown origin, and requires individualized care. The aforementioned recommendations do not apply to these cases, as the standard of care has not been established for patients with implant-associated ALCL. Most patients have been managed by removal of the implant and capsule, and in some cases, with chemotherapy with or without RT.[11,19] It is generally recommended that upon confirmation of ALCL diagnosis, both the implant and capsule should be removed from the affected breast. Decisions to remove the unaffected implant or to treat with chemotherapy and/or RT should be made on an individual basis according to the extent of disease involvement.

Follow-up Therapy

All patients (except for those with ALK-positive ALCL) undergo interim restaging following initial therapy by repeating all prior positive studies. If a PET-CT scan is positive, rebiopsy is recommended before changing course of treatment. Patients are then divided into three groups according to treatment response (CR, PR or no response or progressive disease). Subsequent treatment options depend on whether the patient initially presented with Stage I-II or Stage III-IV disease.

Stage I or II disease (aaIPI low/low-intermediate)

In patients showing CR after interim restaging, planned RT is completed. RT or HDT/ASCR with or without RT is considered for patients showing PR at interim staging. Clinical trials including allogeneic transplant or RT is another option for this group of patients. End-of-treatment restaging is performed after completion of treatment. No further treatment is necessary for those showing CR; these patients can be monitored by follow up every 3-6 months for 5 years, and then yearly as clinically indicated. Patients with PR at end-of-treatment restaging and those with no response or progressive disease following initial or follow-up therapy are treated as described for relapsed or refractory disease.

Stage I or II disease (aaIPI high-intermediate/high) or stage III-IV

Patients with a CR can be observed or can be consolidated with HDT/ASCR. Local RT can be given prior to or following HDT. Patients with PR or no response or progressive disease after initial therapy are treated similarly to patients with relapsed or refractory disease.

Treatment for Relapsed or Refractory Disease

Several retrospective studies have evaluated the role of HDT/ASCR in patients with relapsed or refractory PTCL.[44,59-63] In patients with relapsed or primary refractory PTCL (N=36) undergoing HDT/ASCR, the 3-year

EFS and OS rates were 37% and 48%, respectively, which appeared similar to outcomes of patients with relapsed diffuse large B-cell lymphoma (DLBCL) who received HDT/ASCR in a retrospective comparison (42% and 53%, respectively).[62] In another retrospective study of patients with relapsed or primary refractory PTCL (N=24; excluding patients with ALK-positive ALCL) who received HDT/ASCR, the 5-year PFS and OS rates were 24% and 33%, respectively; these outcomes also appeared similar to outcomes in patients with relapsed DLBCL (34% and 39%, respectively).[60] Aggressive second-line chemotherapy with ICE followed by HDT/ASCR was evaluated in patients with relapsed/refractory PTCL.[59] Among 40 patients treated with ICE, 27 (68%) underwent HDT/ASCR. Based on intent-to-treat analysis, median PFS was 6 months from the time of last ICE therapy; 70% of patients relapsed within 1 year. Patients with relapsed disease had significantly higher 3-year PFS rate compared with those who were primary refractory (20% vs. 6%; *P*=0.0005).[59] Nevertheless, salvage therapy for patients with relapsed/refractory PTCL remains suboptimal, even with the incorporation of HDT/ASCR. In a retrospective review of patients with PTCL who underwent HDT/ASCR at Stanford University (N=53), the 5-year PFS rates for patients in first CR/PR, CR/PR after second-line therapy and those with refractory disease were 51%, 12%, and 0%, respectively; the 5-year OS rates were 76%, 40%, and 30%, respectively.[63] The disease status and the number of prior regimens received prior to transplant were significant prognostic factors. In a retrospective analysis of data from the Spanish Group for Lymphoma and Autologous Transplantation (GEL-TAMO) registry (N=115), the 5-year OS rate was 45% for the group of patients with PTCL treated with HDT/ASCR in the salvage setting (n=78) compared with 80% for those who were transplanted in first CR (n=37) (*P*=0.007).[61] Within the group of patients in the salvage setting, the 5-year OS rates for patients who underwent HDT/ASCR in first PR, CR at second-line or later lines of therapy, or with refractory disease, were 46%, 54%, and 0%, respectively.[61] In an analysis of data from CIBMTR that evaluated outcomes with HDT/ASCR and allogeneic stem cell transplantation (SCT) in patients with T-cell lymphomas (N=241; ALCL, 46%; PTCL, 42%), HDT/ASCR resulted in improved outcomes compared with allogeneic SCT for the subgroup of patients with ALCL histology but not for other histologies.[64] Among patients with ALCL (n=111), HDT/ASCR resulted in significantly higher 3-year PFS (55% vs. 35%; *P*=0.03) and OS (68% vs. 41%; *P*=0.003) compared with allogeneic SCT. Survival outcomes with HDT/ASCT appeared less favorable for patients with PTCL-NOS (n=102), and no significant differences in outcomes were observed between HDT/ASCR and allogeneic SCT with regards to 3-year PFS (29% vs. 33%) or OS (45% vs. 42%) in this subgroup.[64] For patients who received transplantation beyond first CR, HDT/ASCR resulted in numerically higher 3-year PFS (41% vs. 33%) and OS (53% vs. 41%) compared with allogeneic SCT, but these differences were not statistically significant; cumulative incidence of non-relapse mortality was higher with allogeneic SCT compared with HDT/ASCR in patients transplanted beyond first CR (*P*<0.001).[64] Thus, these findings suggest that HDT/ASCR as first-line consolidation therapy may be associated with a durable survival benefit, while this treatment modality only infrequently results in durable benefit in patients with relapsed or refractory disease—possibly with the exception of patients with relapsed ALCL. Additional data are awaited from the CIBMTR analysis.

Recent reports have shown that allogeneic SCT may provide an option for patients with relapsed or refractory PTCL. In a retrospective analysis of data from the French registry for patients who received allogeneic SCT (N=77; PTCL-NOS 35%; ALCL 35%; AITL 14%), the 5-year EFS and OS rates were 53% and 57%, respectively.[65] The 5-year transplant-related mortality (TRM) rate was 34%; TRM at 100 days was 21%.

Patients had previously received a median of 2 prior therapies (range, 1-5), and 74% had received myeloablative conditioning prior to transplantation.[65] Patients who received ≤2 lines of prior chemotherapy had significantly higher 5-year OS rate compared with those who received >2 lines (73% vs. 39%; *P*=0.003). The 5-year OS rate was also significantly higher among patients transplanted in remission (CR or PR) compared with those who were transplanted with less than a PR (69% vs. 29%; *P*=0.0003). No significant differences in outcomes (OS, EFS, or TRM) were observed between types of conditioning regimen. Based on multivariate analysis, resistant disease (less than PR) at the time of transplantation and severe acute graft-versus-host disease (GVHD) were significant independent predictors for worse survival outcomes.[65] In the aforementioned analysis of data from the CIBMTR database for patients with T-cell lymphomas undergoing transplantation (N=241; PTCL, 42%), outcomes with HDT/ACSR (n=115) and allogeneic SCT (n=126; myeloablative conditioning in 59%) were reported.[64] A higher percentage of patients undergoing HDT/ASCR had ALCL histology, chemosensitive disease, and were transplanted in first CR, compared with patients undergoing allogeneic SCT. The TRM rate at 100 days was 2% for the HDT/ASCR group compared with 17% for the allogeneic SCT group. For the group of patients who were transplanted in the salvage setting (i.e., less than first CR), the 3-year OS rate was 53% with HDT/ASCR compared with 41% with allogeneic SCT.[64] In a recent analysis of single-institution data from the M.D. Anderson Cancer Center, outcomes were reported for patients with T-cell lymphomas (N=196; PTCL-NOS, n=61; ALCL, n=50; AITL, n=19) who underwent HDT/ASCR (n=119) or allogeneic SCT (n=77; myeloablative conditioning in 75%).[66] Among the patients who underwent HDT/ASCR, PFS and OS rates were 30% and 39%, respectively, after a median follow up of 39 months. Among the patients who underwent allogeneic SCT, the PFS and OS rates were 30% and 43%, respectively, after a median follow up of 65 months. Among the subgroup of patients in the allogeneic SCT group who had nodal T-cell lymphoma (PTCL-NOS, ALCL, or AITL), the 3-year PFS and OS rates were 23% and 38%, respectively. The patients in this latter subgroup were primarily (87%) transplanted in the salvage setting (i.e., less than first CR).[66] Collectively, these findings from retrospective analyses of data point to a 3-year OS rate of about 40% in patients who undergo allogeneic SCT (primarily with myeloablative conditioning) for relapsed or refractory PTCL. However, the early TRM rates are high with this procedure, with a reported 100-day TRM rate of about 20%.

Other studies have evaluated the role of allogeneic SCT using reduced intensity conditioning (RIC) in patients with relapsed/refractory PTCL. In a phase II study, Corradini et al investigated the role of RIC allogeneic SCT in patients with relapsed or refractory PTCL (N=17).[67] The estimated 3-year PFS and OS rates were 64% and 81%, respectively. Donor lymphocyte infusion induced responses in some patients progressing after allografting. The estimated probability of non-relapse mortality (NRM) at 2 years was 6%.[67] A recent study reporting on retrospective analysis of long-term data from patients with relapsed/refractory PTCL treated with RIC allogeneic SCT (N=52; PTCL-NOS, n=23; ALCL, n=11; AITL, n=9) showed 5-year PFS and OS rates of 40% and 50%, respectively.[68] The 5-year NRM rate was 12%, and extensive chronic GVHD was associated with increased risks for NRM. The 5-year cumulative relapse rate was 49%; worse disease status at the time of transplantation and greater lines of prior therapy were associated with higher relapse risks.[68] A retrospective study of data from the EBMT database demonstrated that allogeneic SCT induced long-term remissions in patients with AITL (N=45; 62% of patients had ≥2 lines of therapy prior to transplantation) .[69] Myeloablative conditioning was employed in 56% of patients while the

remaining patients received RIC. The cumulative NRM rate at 1 year was 25%; these rates were similar between myeloablative conditioning (29%) and RIC (24%). The estimated 3-year relapse rate was 20%. The 3-year PFS and OS rates were 54% and 64%, respectively. These outcomes were not significantly different between conditioning regimens.[69] Patients with chemotherapy-sensitive disease had a significantly higher rate PFS compared with those with refractory disease (66% vs. 33%, respectively). Further prospective data are needed to determine the role of allogeneic SCT (either with myeloablative conditioning or RIC) in patients with relapsed/refractory PTCL.

Until recently, data to guide the treatment of patients with relapsed and refractory PTCL came from small series of patients treated with various single agents. Many of the drugs used are extrapolated from the following reports; gemcitabine[70-72] and alemtuzumab [73,74] have shown activity in such experiences. Zinzani et al recently reported the outcome of patients with relapsed/refractory T-cell lymphoma (N=39) treated with gemcitabine (on days 1, 8, and 15 on a 28-day schedule; 1200 mg/m/day for a total of three to six cycles). Among the subgroup of 20 patients with PTCL-NOS, the ORR was 55% (CR 30%); 5 of these patients were in continuous CR with a median duration of CR of 34 months (range, 15-60 months).[72] In a pilot study, alemtuzumab at standard dose schedule produced an ORR of 36% (CR 21%) among patients with relapsed or chemotherapy-refractory PTCLs (N=14).[73] However, alemtuzumab therapy was associated with significant hematologic toxicity and infectious complications, including 5 deaths due to opportunistic infections.[73] The preliminary results of another phase II study showed that in patients with pretreated T-cell lymphoma (N=10; PTCL, n=6), alemtuzumab at a reduced dose was less toxic and as equally effective as the standard dose used in the prior pilot study.[74] The ORR was 60% (CR 20%). In the subset of patients with PTCL-NOS, ORR was 50% (CR 33%). CMV reactivation was observed only in 10% of patients, as compared with 42% of the patients reported by Enblad et al. The median duration of response was 7 months.[74]

Pralatrexate is a new antifolate with a high affinity for reduced folate carrier type 1 (RFC-1), and has shown significant activity in patients with relapsed/refractory T-cell lymphoma.[75-77] Results from the pivotal, international, phase II study (PROPEL) showed that pralatrexate resulted in an ORR of 29% (CR 11%; response assessed by an independent central review) in pretreated patients with relapsed or refractory PTCL (N=109 evaluable).[76,78] Patients on this study had received a median of 3 prior systemic therapies (range, 1-12); moreover, 63% were refractory to their most recent prior therapy, 24% had never responded to any prior therapy, and 16% had received prior autologous SCT. The median duration of response was 10 months. For all patients, the median PFS and OS were 3.5 months and 14.5 months, respectively.[76] The most common grade 3-4 adverse events included thrombocytopenia (32%), neutropenia (22%), anemia (18%), and mucositis (22%).[76] In September 2009, , pralatrexate became the first FDA-approved single agent for the treatment of patients with relapsed or refractory PTCL.

Romidepsin is a histone deacetylase (HDAC) inhibitor with single-agent activity in patients with relapsed or refractory CTCL and PTCL. In the pivotal multicenter phase II study, romidepsin induced responses in patients with relapsed/refractory PTCL (N=130 evaluable).[79,80] Patients on this study had received a median of 2 prior systemic therapies (range, 1-8), and 16% had failed prior autologous HSCT. The ORR was 25% (CR/CRu 15%; response evaluated by an independent review committee); the ORR and CR/CRu rate by investigator assessment was 39% and 16%, respectively.[80] Median duration of response was 17

months. The median PFS for all patients was 4 months; median PFS for patients with a CR/CRu was 18 months. The most common grade ≥3 adverse events included thrombocytopenia (24%), neutropenia (20%), and infections (19% for any; including pneumonia [5%] and sepsis [5%]).[79,80] In another multicenter phase II study, romidepsin was evaluated in patients with previously treated PTCL (N=47; PTCL-NOS, 57%; AITL, 15%; ALCL, 8.5%).[81] Patients had received a median of 3 prior therapies (range, 1-11), including SCT in 38% of patients. The ORR was 38% (CR 18%) and the median duration of response was 8.9 months. Among responding patients, the median time to progression was 13 months.[81] Romidepsin was approved by the FDA in June 2011 for the treatment of patients with relapsed PTCL.

Brentuximab vedotin is an antibody-drug conjugate that targets CD30-expressing malignant cells by binding to CD30 on the cell surface. After internalization, a potent antimicrotubule agent (monomethyl auristatin E) is released within the cell.[82,83] A multicenter phase II study evaluated brentuximab vedotin (IV 1.8 mg/kg every 3 weeks, up to 16 cycles) in patients with relapsed or refractory systemic ALCL (N=58). Patients had received a median of 2 prior systemic therapies (range, 1–6) and 62% were considered to have primary refractory disease; in addition, 50% of patients were refractory to their most recent prior therapy and 22% had never responded to any therapy.[84] The ORR was 86% (evaluated by an independent review committee) with CR in 57% of patients. The median duration of response was approximately 13 months. The median PFS for all patients was 13 months; the median OS has not been reached with current follow up.[84] The most common grade 3 or 4 adverse events reported in this study included neutropenia (21%), thrombocytopenia (14%), and peripheral sensory neuropathy (12%).[84] No treatment-related deaths were reported. Based upon the results from this study, brentuximab vedotin was approved by the FDA (August 2011) for treating patients with systemic ALCL after failure of at least one prior multiagent chemotherapy regimen. This agent has not been evaluated in patients with relapsed/refractory cutaneous ALCL and therefore cannot be recommended for those patients at this time.

Bendamustine is an alkylating agent with a purine-like benzimidazole ring component, and is currently indicated for the treatment of patients with indolent NHL refractory to prior rituximab-containing regimen, and those with chronic lymphocytic leukemia (CLL). This agent was recently evaluated in a multicenter phase II study (BENTLEY trial) in patients with relapsed or refractory PTCL (N=60; AITL, 53%; PTCL-NOS, 38%).[85] Patients had received a median of 1 prior therapy (range, 1–3) and 45% were considered refractory to their last therapy; 92% had received prior CHOP or CHOP-like regimens. The ORR after 3 cycles of bendamustine was 50% with CR (including CRu) in 28% of patients. Forty patients (67%) had completed 3 or more cycles of bendamustine; 25% received all 6 cycles of therapy. The median duration of response was short, at only 3.5 months.[85] The median PFS and OS for all patients was 3.6 months and 6.3 months, respectively. The most common grade 3 or 4 toxicity included neutropenia (30%), thrombocytopenia (24%), and infectious events (20%).[85]

NCCN Recommendations

Patients who are candidates for transplant can be treated with second-line chemotherapy prior to transplant. Consolidation therapy with HDT/ASCR or allogeneic HSCT is recommended for those with a CR or PR. Localized areas can be treated with RT before or after high-dose therapy. Patients who are not candidates for transplant are treated with second-line regimens or palliative RT. Suggested treatments include alemtuzumab, bortezomib, brentuximab vedotin (for patients with systemic ALCL only), cyclosporine (for patients with refractory AITL only), dose-adjusted EPOCH, gemcitabine, pralatrexate,

or romidepsin. Participation in a clinical trial is strongly preferred for these patients. In patients receiving romidepsin, serum potassium and magnesium levels should be monitored to minimize any risk of ECG abnormalities.

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