NCCN Guidelines® Insights
Non-Hodgkin's Lymphomas, Version 3.2016
Featured Updates to the NCCN Guidelines

Steven M. Horwitz, MD[1,*]; Andrew D. Zelenetz, MD, PhD[1*]; Leo I. Gordon, MD[2*]; William G. Wierda, MD, PhD[3*]; Jeremy S. Abramson, MD[4]; Ranjana H. Advani, MD[5]; C. Babis Andreadis, MD, MSCE[6]; Nancy Bartlett, MD[7]; John C. Byrd, MD[8]; Luis E. Fayad, MD[3]; Richard I. Fisher, MD[9]; Martha J. Glenn, MD[10]; Thomas M. Habermann, MD[11]; Nancy Lee Harris, MD[4]; Francisco Hernandez-Ilizaliturri, MD[12]; Richard T. Hoppe, MD[5]; Mark S. Kaminski, MD[13]; Christopher R. Kelsey, MD[14]; Youn H. Kim, MD[5]; Susan Krivacic, MPAff[15]; Ann S. LaCasce, MD[16]; Matthew Lunning, DO[17]; Auayporn Nademanee, MD[18]; Oliver Press, MD, PhD[19]; Rachel Rabinovitch, MD[20]; Nishitha Reddy, MD[21]; Erin Reid, MD[22]; Kenneth Roberts, MD[23]; Ayman A. Saad, MD[24]; Lubomir Sokol, MD, PhD[25]; Lode J. Swinnen, MB, ChB[26]; Julie M. Vose, MD, MBA[17]; Joachim Yahalom, MD[1]; Nadeem Zafar, MD[27]; Mary Dwyer, MS, CGC[28*]; Hema Sundar, PhD[28*]; and Pierluigi Porcu, MD[8*]

Abstract

Peripheral T-cell lymphomas (PTCLs) represent a relatively uncommon heterogeneous group of non-Hodgkin's lymphomas (NHLs) with an aggressive clinical course and poor prognosis. Anthracycline-based multiagent chemotherapy with or without radiation therapy followed by first-line consolidation with high-dose therapy followed by autologous stem cell rescue (HDT/ASCR) is the standard approach to most of the patients with newly diagnosed PTCL. Relapsed or refractory disease is managed with second-line systemic therapy followed by HDT/ASCR or allogeneic stem cell transplant, based on the patient's eligibility for transplant. In recent years, several newer agents have shown significant activity in patients with relapsed or refractory disease across all 4 subtypes of PTCL. These NCCN Guideline Insights highlight the important updates to the NCCN Guidelines for NHL, specific to the management of patients with relapsed or refractory PTCL.

J Natl Compr Canc Netw 2016;14(9):1067–1079

From [1]Memorial Sloan Kettering Cancer Center; [2]Robert H. Lurie Comprehensive Cancer Center of Northwestern University; [3]The University of Texas MD Anderson Cancer Center; [4]Massachusetts General Hospital Cancer Center; [5]Stanford Cancer Institute; [6]UCSF Helen Diller Family Comprehensive Cancer Center; [7]Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; [8]The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute; [9]Fox Chase Cancer Center; [10]Huntsman Cancer Institute at the University of Utah; [11]Mayo Clinic Cancer Center; [12]Roswell Park Cancer Institute; [13]University of Michigan Comprehensive Cancer Center; [14]Duke Cancer Institute; [15]Consultant; [16]Dana-Farber/Brigham and Women's Cancer Center; [17]Fred & Pamela Buffett Cancer Center; [18]City of Hope Comprehensive Cancer Center; [19]Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance; [20]University of Colorado Cancer Center; [21]Vanderbilt-Ingram Cancer Center; [22]UC San Diego Moores Cancer Center; [23]Yale Cancer Center/Smilow Cancer Hospital; [24]University of Alabama at Birmingham Comprehensive Cancer Center; [25]Moffitt Cancer Center; [26]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; [27]St. Jude Children's Research Hospital/University of Tennessee Health Science Center; and [28]National Comprehensive Cancer Network

*Provided content development and/or authorship assistance.

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines® Insights highlight important changes to the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the NCCN Guideline Panel discussion, including the literature reviewed.**

These NCCN Guidelines Insights do not represent the full NCCN Guidelines; further, the National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding the content, use, or application of the NCCN Guidelines and NCCN Guidelines Insights and disclaims any responsibility for their applications or use in any way.

The full and most current version of these NCCN Guidelines are available at NCCN.org.

NCCN: Continuing Education

Accreditation Statement

This activity has been designed to meet the educational needs of physicians, nurses, and pharmacists involved in the management of patients with cancer. There is no fee for this article. The National Comprehensive Cancer Network (NCCN) is accredited by the ACCME to provide continuing medical education for physicians. NCCN designates this journal-based CE activity for a maximum of 1.0 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

NCCN is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center`s Commission on Accreditation.

NCCN designates this educational activity for a maximum of 1.0 contact hour. Accreditation as a provider refers to recognition of educational activities only; accredited status does not imply endorsement by NCCN or ANCC of any commercial products discussed/displayed in conjunction with the educational activity. Kristina M. Gregory, RN, MSN, OCN, is our nurse planner for this educational activity.

National Comprehensive Cancer Network is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. NCCN designates this continuing education activity for 1.0 contact hour(s) (0.1 CEUs) of continuing education credit in states that recognize ACPE accredited providers. This is a knowledge-based activity. UAN: 0836-0000-16-009-H01-P

All clinicians completing this activity will be issued a certificate of participation. To participate in this journal CE activity: 1) review the learning objectives and author disclosures; 2) study the education content; 3) take the posttest with a 66% minimum passing score and complete the evaluation at **http://education.nccn.org/node/79463;** and 4) view/print certificate.

Release date: September 1, 2016; Expiration date: September 1, 2017

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to NCCN Guidelines for Non-Hodgkin's Lymphomas
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Non-Hodgkin's Lymphomas

Disclosure of Relevant Financial Relationships

Editor:

Kerrin M. Green, MA, Assistant Managing Editor, *JNCCN—Journal of the National Comprehensive Cancer Network*, has disclosed that she has no relevant financial relationships.

CE Authors:

Deborah J. Moonan, RN, BSN, Director, Continuing Education, NCCN, has disclosed that she has no relevant financial relationships.

Kristina M. Gregory, RN, MSN, OCN, Vice President, Clinical Information Operations, NCCN, has disclosed that she has no relevant financial relationships.

Rashmi Kumar, PhD, Senior Manager, Clinical Content, NCCN, has disclosed that she has no relevant financial relationships.

Individuals Who Provided Content Development and/or Authorship Assistance:

Steven M. Horwitz, MD, Panel Member, has disclosed that he receives grant/research support from Amgen Inc., Celgene Corporation, Infinity Pharmaceuticals, Kyowa Hakko Kirin Co., Ltd., Millennium Pharmaceuticals, Inc., Seattle Genetics, and Spectrum Pharmaceuticals; he receives consulting fees/honoraria from Celgene Corporation, HUYA Bioscience International, Infinity Pharmaceuticals, Janssen Pharmaceutica Products, LP, Seattle Genetics, and Spectrum Pharmaceuticals; and is a scientific advisor for Kyowa Hakko Kirin Co., Ltd. and Millennium Pharmaceuticals, Inc.

Andrew D. Zelenetz, MD, PhD, Panel Chair, has disclosed that he receives consulting fees/honoraria from Amgen Inc.; Axess Oncology; Celgene Corporation; Gilead Sciences, Inc.; GlaxoSmithKline; Hospira, Inc.; Janssen Pharmaceutica Products, LP; Medscape, LLC; Roche Laboratories, Inc.; Takeda Pharmaceuticals North America, Inc.; and The France Foundation. He receives grant/research support from Bristol-Myers Squibb Company, Gilead Sciences, Inc., GlaxoSmithKline; Janssen Pharmaceutica Products, LP, and Roche Laboratories, Inc.

Leo I. Gordon, MD, Panel Vice-Chair, has disclosed that he is a scientific advisor for Aura Sense Therapeutics.

William G. Wierda, MD, PhD, Panel Vice-Chair, has disclosed that he receives consulting fees/honoraria from AbbVie; Ascerta; Celgene Corporation; Emergent BioSolutions Inc.; Genentech, Inc; Genzyme Corporation; Gilead Sciences; GlaxoSmithKline; Karyopharm Therapeutics Inc.; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; Pharmacyclics, Inc.; Roche Laboratories, Inc.; and sanofi-aventis U.S. He receives grant/research support from and is a scientific advisor for AbbVie, Ascerta, Emergent BioSolutions Inc.; Genentech, Inc.; Gilead Sciences; GlaxoSmithKline; Karyopharm Therapeutics Inc.; Novartis Pharmaceuticals Corporation; Pharmacyclics, Inc.; Roche Laboratories, Inc. He is a scientific advisor for Celgene Corporation, Genzyme Corporation, Merck & Co., Inc., and sanofi-aventis U.S.; and receives grant/research support from Juno Therapeutics and Kite Pharma, Inc.

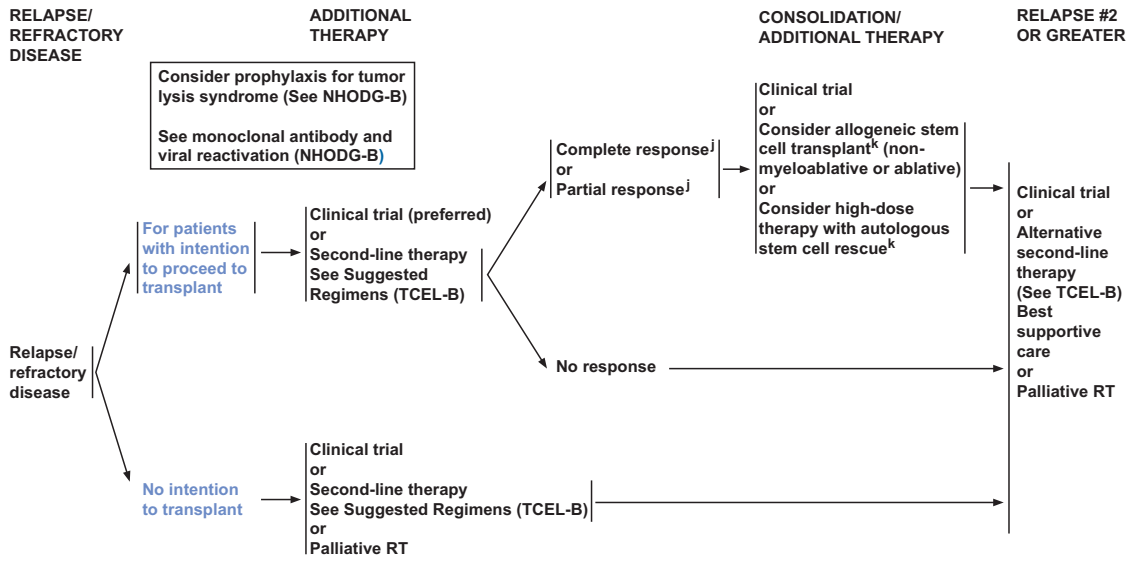
Pierluigi Porcu, MD, Panel Member, has disclosed that he is a scientific advisor for Kyowa Hakko Kirin Co., Ltd. and Actelion Pharmaceuticals Ltd. He has received honoraria/consulting fees from Celgene Corporation; and research support from Infinity Pharmaceuticals, Innate Pharma S.A., Kyowa Hakko Kirin Co., Ltd, miRagen Therapeutics, Seattle Genetics, and Shape Pharmaceuticals, Inc.

Mary Dwyer, MS, CGC, Senior Manager, Guidelines, NCCN, has disclosed that she has no relevant financial relationships.

Hema Sundar, PhD, Oncology Scientist/Senior Medical Writer, NCCN, has disclosed that she has no relevant financial relationships.

This activity is supported by educational grants from AstraZeneca, Bayer Healthcare Pharmaceuticals Inc., Bristol-Myers Squibb, Clovis Oncology, Foundation Medicine, Genentech, Novartis Oncology, Otsuka America Pharmaceutical, Inc., Seattle Genetics, Inc., and Takeda Oncology; support provided by Actelion Pharmaceuticals US, Inc.; and by an independent educational grant from Astellas and Medivation, Inc.

Non-Hodgkin's Lymphoma, Version 3.2016



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

TCEL-4

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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

Overview

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of lymphoproliferative disorders arising from mature T cells of post-thymic origin.[1] PTCLs represent a relatively uncommon group of hematologic malignancies within non-Hodgkin's lymphomas (NHLs) and account for approximately 10% of all NHL cases.[2] PTCL not otherwise specified (PTCL-NOS; 26%) is the most common subtype, followed by angioimmunoblastic T-cell lymphoma (AITL; 18.5%), ALK-positive anaplastic large cell lymphoma (ALCL; 7%), ALK-negative ALCL (6%), and enteropathy-associated T-cell lymphoma (<5%).[3] Recent molecular and genetic studies have identified molecular subgroups of ALK-negative ALCL and PTCL-NOS with distinct clinical outcomes (ALK-negative ALCL with dual-specificity phosphatase 22 [DUSP22] rearrangements and PTCL-NOS characterized by high expression of GATA3 or TBX21).[4,5] Breast implant–associated

SUGGESTED TREATMENT REGIMENS FOR PTCL-NOS AND EATL[a]

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

Alternative Regimens
- Single agents (alphabetical order)
  - Bendamustine
  - Gemcitabine
  - Lenalidomide
- Combination regimen
  - GVD (gemcitabine, vinorelbine, liposomal doxorubicin)[d]

Second-line Therapy (no intention to transplant) and Subsequent Therapy:
- Clinical trial preferred
- Preferred single agents (alphabetical order)
  - Belinostat
  - Brentuximab vedotin for CD30+ PTCL
  - Pralatrexate
  - Romidepsin

Alternative single agents (alphabetical order)
- Alemtuzumab
- Bendamustine
- Bortezomib[e] (category 2B)
- Gemcitabine
- Lenalidomide
- Radiation therapy

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

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

[a]See references for regimens TCEL-B 5 of 5.
[d]Data suggest there may be excessive pulmonary toxicity with GVD (gemcitabine, vinorelbine, liposomal doxorubicin) regimen when used in combination with unconjugated anti-CD30 monoclonal antibodies for the treatment of Hodgkin lymphoma (Blum KA, Jung SH, Johnson JL, et al. Ann Oncol 2010;21:2246-2254). A similar regimen, gemcitabine and liposomal doxorubicin, may be used for mature T-cell lymphoma; however, it is recommended to wait 3–4 weeks following treatment with brentuximab vedotin before initiation.
[e]Activity has been demonstrated in small clinical trials and additional larger trials are needed.

ALCL has also been recently reported to be a distinct entity from systemic ALCL.[6–12]

PTCLs are less responsive to and have less frequent durable remissions with standard combination chemotherapy regimens, and thus carry a poorer prognosis compared with diffuse large B-cell lymphomas (DLBCLs). 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 decreases with older age and higher prognostic risk scores.[13–17] CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone) is the most commonly used first-line regimen for patients with PTCL. However, except for those with ALK-positive ALCL, outcomes are disappointing for patients with the most common forms of PTCLs, namely PTCL-NOS and AITL, compared with the favorable results achieved with DLBCL.[15,17] Chemotherapy regimens that are more intensive than CHOP have not shown any significant improvement in the overall survival (OS) of patients with PTCL, except those with ALCL.[18–21] First-line consolidation with high-dose therapy followed by autologous stem cell rescue (HDT/ASCR) is associated with improved outcomes in patients who experience a good response to induction therapy.[22,23] Second-line systemic therapy followed by HDT/ASCR or allogeneic stem cell transplant (SCT), based on the patient's eligibility for transplant, is the standard treatment approach for patients with relapsed or refractory disease. The management of patients with relapsed/refractory PTCL, however, remains suboptimal.[24]

These NCCN Guidelines Insights highlight the major discussion points regarding the recommendations for the management of patients with relapsed or refractory PTCL.

SUGGESTED TREATMENT REGIMENS FOR AITL[a]

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

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

Second-line Therapy (no intention to transplant) and Subsequent Therapy:
- Clinical trial preferred
- Preferred single agents (alphabetical order)
  - Belinostat
  - Romidepsin

Alternative single agents/regimens (alphabetical order)
- Alemtuzumab
- Bendamustine
- Bortezomib[e] (category 2B)
- Cyclosporine[g]
- Gemcitabine
- Lenalidomide
- Pralatrexate[f]
- Radiation therapy

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

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

[a]See references for regimens TCEL-B 5 of 5.
[e]Activity has been demonstrated in small clinical trials and additional larger trials are needed.
[f]In AITL, pralatrexate has limited activity.
[g]With close follow-up of renal function.

Management of Relapsed/Refractory PTCL

Role of Transplant

HDT/ASCR in patients with relapsed or refractory PTCL-NOS been evaluated in several retrospective studies.[25–29] Although HDT/ASCR has been reported to result in survival rates comparable to those of DLBCL in patients with chemosensitive relapsed/refractory PTCL, one retrospective analysis of outcomes based on major PTCL subtypes showed that event-free survival (EFS) rates were inferior in patients with PTCL-NOS (23%; *P*=.028) and that those with ALCL had a nonsignificant trend toward improved EFS rates (67%; *P*=.41).[25] In another 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 patients with PTCL treated with HDT/ASCR in the second-line setting (n=78) compared with 80% for those who received a transplant in their first complete response (CR; n=37; *P*=.007).[26] For the patients treated in the second-line setting, 5-year OS rates for those who underwent HDT/ASCR in first partial remission (PR), those who experienced CR at second-line or later lines of therapy, or those with refractory disease were 46%, 54%, and 0%, respectively.[26] The number of regimens received before transplant, having chemosensitive disease at the time of transplant, and the second-line age-adjusted international prognostic index have been identified as significant prognostic factors for clinical outcome.[27–29]

Recent reports have shown that allogeneic SCT using myeloablative conditioning or reduced-intensity conditioning (RIC) may provide an option for patients with relapsed or refractory PTCL.[30–33] In a phase II study, Corradini et al[30] investigated the role of RIC allogeneic SCT in patients with relapsed or refractory PTCL (N=17); estimated 3-year progression-free sur-

SUGGESTED TREATMENT REGIMENS FOR ALCL[a]

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

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

Second-line Therapy (no intention to transplant) and Subsequent Therapy:
- Clinical trial preferred
- Preferred single agents (alphabetical order)
  - Belinostat
  - Brentuximab vedotin
  - Pralatrexate
  - Romidepsin

Alternative single agents/regimens (alphabetical order)
- Alemtuzumab
- Bendamustine
- Bortezomib[e] (category 2B)
- Gemcitabine
- Radiation therapy

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

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

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

vival (PFS) and OS rates were 64% and 81%, respectively. Donor lymphocyte infusion induced responses in some patients whose disease progressed after allografting. The estimated probability of nonrelapse mortality (NRM) at 2 years was 6%.[30] In a retrospective analysis of data from the French registry of patients who received allogeneic SCT with myeloablative conditioning (N=77; PTCL-NOS, 35%; ALCL, 35%; AITL, 14%), the 5-year EFS and OS rates were 53% and 57%, respectively.[31] The 5-year transplant-related mortality rate was 34% and at 100 days was 21%. Patients had previously received a median of 2 prior therapies (range, 1–5), and 74% had received myeloablative conditioning before transplantation.[31] Those who received 2 or fewer lines of prior chemotherapy had significantly higher 5-year OS rates compared with those who received more than 2 lines (73% vs 39%; *P*=.003). The 5-year OS rate was also significantly higher among patients who underwent a transplant in remission (CR or PR) compared with those who received a transplant with less than a PR (69% vs 29%; *P*=.0003). No significant differences in outcomes (OS, EFS, or transplant-related mortality) were observed between types of conditioning regimen. Based on multivariate analysis, resistant disease at the time of transplantation and severe acute graft-versus-host disease were significant independent predictors of worse survival outcomes. A retrospective study of data from the European Society for Blood and Marrow Transplantation database showed that allogeneic SCT induced long-term remissions in patients with AITL (N=45; 62% had ≥2 lines of therapy before transplantation).[32] Myeloablative conditioning was performed in 56% of patients and the remainder underwent 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%, and 3-year PFS and OS rates

Non-Hodgkin's Lymphomas, Version 3.2016

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 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.

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.

GND (gemcitabine, vinorelbine, liposomal doxorubicin)

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

GemOX (gemcitabine, oxaliplatin)

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

ICE (ifosfamide, carboplatin, etoposide)

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

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.S

TCEL-B
5 OF 5

were 54% and 64%, respectively. These outcomes were not significantly different between conditioning regimens.[32] Patients with chemosensitive disease had a significantly higher PFS rate compared with those with refractory disease (66% vs 33%, respectively). A retrospective analysis of long-term data from patients with relapsed/refractory PTCL treated with RIC allogeneic SCT (N=52; PTCL-NOS, n=23; ALCL, n=11; AITL, n=9) showed 5-year PFS and OS rates of 40% and 50%, respectively.[33] The 5-year NRM rate was 12%, and extensive chronic graft-versus-host disease was associated with increased risk for NRM. The 5-year cumulative relapse rate was 49%; worse disease status at time of transplantation and more lines of prior therapy were associated with higher relapse risks.[33]

In an analysis of data from the Center for International Blood and Marrow Transplant Research that evaluated outcomes with HDT/ASCR and allogeneic SCT in patients with T-cell lymphomas (n=241: ALCL, 112; PTCL, 102; and AITL, 27), HDT/ASCR resulted in improved outcomes compared with allogeneic SCT for the subgroup of patients with ALCL, but not for other subtypes.[34] Among patients with ALCL (n=111), HDT/ASCR resulted in significantly higher 3-year PFS (55% vs 35%; *P*=.03) and OS rates (68% vs 41%; *P*=.003) with significantly reduced NRM and overall mortality compared with allogeneic SCT. Survival outcomes with HDT/ASCR seemed less favorable for those with PTCL-NOS (n=102), and no significant differences in outcomes were observed between HDT/ASCR and allogeneic SCT with regard to 3-year PFS (29% vs 33%) or OS rates (45% vs 42%) in this subgroup. The overall NRM rate for all patients at 100 days was 2% for the HDT/ASCR group compared with 19% for the myeloablative allogeneic SCT group and 18% for the RIC allogeneic SCT. A higher percentage of patients undergoing HDT/

ASCR had ALCL histology and chemosensitive disease, and received a transplant at first CR. Allogeneic SCT recipients had more bone marrow involvement, more lines of chemotherapy before transplant, extranodal disease at diagnosis, and a higher second-line prognostic index at transplantation. For patients who received a transplant in the salvage setting (ie, less than first CR), 3-year OS rates were 53%, 31%, and 50%, respectively. For patients who received a transplant after first CR, HDT/ASCR resulted in numerically higher 3-year PFS (41% vs 33%) and OS rates (53% vs 41%) compared with allogeneic SCT, but these differences were not statistically significant; cumulative incidence NRM was higher with allogeneic SCT compared with HDT/ASCR in patients transplanted after first CR ($P<.001$).

In a recent analysis of single-institution data from the MD Anderson Cancer Center, outcomes were reported for 134 patients with T-cell lymphomas who underwent HDT/ASCR and allogeneic SCT either as frontline consolidation (n=58) or for relapsed disease (n=76).[35] PTCL-NOS and AITL were the dominant histologic types. Among those who underwent HDT/ASCR (n=41) or allogeneic SCT (n=35) for relapsed disease, 4-year OS rates were 50% and 36%, respectively ($P<.05$). The 4-year PFS rates were not statistically significantly different between the 2 groups (38% vs 28%). The 4-year OS rates were 59% and 53%, respectively, for patients who were in second and third CR at transplant; corresponding survival rates for those in PR were 55% and 22%, respectively. Patients with chemorefractory disease had inferior outcomes compared with those with chemosensitive disease; however, the results were not significantly different between HDT/ASCR and allogeneic SCT. The 4-year OS rates were 29% and 35%, respectively ($P=.6$), and the 4-year PFS rates were 25% and 18%, respectively ($P=.4$). The 4-year NRM rate was significantly higher with allogeneic SCT (40% vs 17% for HDT/ASCR; $P<.001$).

Thus, these findings suggest that HDT/ASCR less frequently results in a durable benefit for patients with relapsed/refractory disease compared with allogeneic SCT. However, this conclusion is not universal in the literature, and those with relapsed ALCL and more chemosensitive relapsed disease appear to benefit from HDT/ASCR more often than those with non-ALCL subtypes and less chemosensitive disease. Allogeneic SCT using RIC may provide a more reliable curative option for most patients with relapsed/refractory PTCL based on eligibility for transplant.[30–33]

Second-Line Systemic Therapy

In prospective randomized studies, PTCLs have been included with aggressive B-cell lymphomas.[36,37] Combination chemotherapy regimens used for relapsed/refractory PTCL are derived from aggressive lymphoma clinical trials that have also included a limited number of patients with PTCL. However, it has not been possible to assess the impact of chemotherapy in this subgroup of patients with PTCLs due to small sample size and very limited data available for the specific use of combination chemotherapy regimens in patients with relapsed/refractory PTCL.[38–41] Aggressive second-line chemotherapy with ICE (ifosfamide, carboplatin, etoposide) followed by HDT/ASCR was evaluated in patients with relapsed/refractory PTCL.[38] 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 experienced relapse within 1 year. Patients with relapsed disease had a significantly higher 3-year PFS rate compared with those who had primary refractory disease (20% vs 6%; $P=.0005$).[38]

Gemcitabine, dexamethasone, and cisplatin (GDP) followed by HDT/ASCR has also been shown to be effective for the treatment of patients with relapsed or refractory PTCL.[39] In a retrospective analysis of 51 patients with relapsed (n=31) or primary refractory (n=20) PTCL identified in the BC Cancer Agency Lymphoid Cancer Database, GDP resulted in an overall response rate (ORR) of 80% (CR, 47%). The 2-year PFS and OS rates were 25% and 43%, respectively, with no differences among the histologic subtypes. The median follow-up was 10.4 months. Among patients who were treated subsequently with HDT/ASCR, the 2-year posttransplant OS rate was 53%, with no difference in survival rates between patients with relapsed and refractory disease ($P=.23$). For all nontransplanted patients, the median PFS and OS after treatment with GDP were 4.4 and 6.8 months, respectively. In another trial that evaluated GDP followed by HDT/ASCR in 25 patients with relapsed/refractory PTCL (14 patients with PTCL-NOS and 4 patients with AITL), the ORR was 72% (48% CR and 24% PR) after a median of 4 cycles of GDP and the median

PFS was 9.3 months.[40] Results of a recent retrospective analysis showed that gemcitabine, vinorelbine, and doxorubicin (GND) was effective and well tolerated by patients with refractory or relapsed T-cell lymphomas (n=49; 28 patients with PTCL-NOS), with an ORR of 65.2% and a median OS of 36 months. The 5-year estimated OS rate was 32.4%.[41]

Until recently, data to guide the treatment of relapsed and refractory PTCL with various single agents (such as alemtuzumab, bortezomib, gemcitabine, lenalidomide, and cyclosporine) came from small single-institution series.

In a pilot study, alemtuzumab at standard dose schedule produced an ORR of 36% (CR, 21%) among patients with relapsed or chemotherapy-refractory PTCLs (n=14).[42] However, alemtuzumab was associated with significant hematologic toxicity and infectious complications, including 5 deaths due to opportunistic infections.[42] 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.[43] In the subset of patients with PTCL-NOS, the ORR was 50% (CR, 33%). The median duration of response was 7 months. Cytomegalovirus reactivation was observed only in 10% of patients, compared with 42% of the patients reported by Enblad et al.[42]

Long-term follow-up data from a small series of 39 patients with pretreated relapsed/refractory T-cell lymphoma showed that single-agent gemcitabine resulted in an ORR of 55% (CR, 30%) in a subgroup of 20 patients with PTCL-NOS; 5 of these patients were in continuous CR with a median response duration of 34 months (range, 15–60 months).[44] Bortezomib also has demonstrated activity in patients with relapsed or refractory cutaneous T-cell lymphomas (CTCL; 10 patients with mycosis fungoides and 2 patients with PTCL-NOS with isolated skin involvement), resulting in an ORR of 67% (17% CR and 50% PR).[45] Histologically, responses were observed in 7 patients with CTCL and one patient with PTCL-NOS with isolated skin involvement. All responses were durable, lasting from 7 to 14 or more months.

Lenalidomide monotherapy has also been effective in the treatment of relapsed or refractory PTCL, resulting in an ORR of 24%. The median OS and PFS were 12 and 4 months, respectively, with a median duration of response of 5 months.[46] The results of a multicenter, single-arm, phase II trial (EXPECT) that evaluated the efficacy of lenalidomide monotherapy in patients with relapsed or refractory PTCL (n=54), showed that lenalidomide was particularly active in patients with relapsed or refractory AITL. The ORR was 22% (11% CR or unconfirmed CR [CRu]) for the entire study population.[47] The median PFS and median duration of response were 2.5 and 3.6 months, respectively, in the intent-to-treat population. Among patients with AITL, the ORR, median PFS, and median duration of response were 31% (15% CR/CRu), 4.6 months, and 3.5 months, respectively.

Cyclosporine has also been reported as treatment option for patients with relapsed AITL.[48,49] In a small series of 12 patients with relapsed/refractory AITL for whom prior steroid therapy or multiagent chemotherapy failed, cyclosporine, at fairly high doses, induced CRs and PRs in 3 and 5 patients, respectively.[48] A more recent case report also demonstrated that cyclosporine is an effective treatment for AITL relapsing after HDT/ASCR.[49]

In recent years, several newer agents, such as pralatrexate, romidepsin, belinostat, and brentuximab vedotin, have demonstrated significant activity in multicenter clinical trials for the management of patients with relapsed or refractory PTCL.

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.[50,51] The pivotal, international, phase II study (PROPEL) evaluated pralatrexate in heavily pretreated patients with relapsed or refractory PTCL (n=109; 59 patients with PTCL-NOS; 13 patients with AITL; and 17 patients with ALCL).[51] Patients on this study had received a median of 3 prior systemic therapies; 63% were refractory to their most recent prior therapy, 24% had never responded to any prior therapy, and 16% had received prior autologous SCT. Pralatrexate resulted in an ORR of 29% (CR, 11%; response assessed by an independent central review). Although 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 2 subtypes (32% and 35%, respectively, for PTCL-NOS and ALCL).[51] The median duration of response was 10 months. For all patients, the median PFS and OS were 3.5 and 14.5 months, respec-

tively. The most common grade 3/4 adverse events included thrombocytopenia (32%), neutropenia (22%), anemia (18%), and mucositis (22%). In September 2009, pralatrexate became the first FDA-approved single agent for the treatment of patients with relapsed or refractory PTCL.

Bendamustine was evaluated in a multicenter phase II study (BENTLEY trial) in patients with relapsed or refractory PTCL (n=60; AITL, 53%; PTCL-NOS, 38%).[52] Patients had received a median of 1 prior therapy (range, 1–3), and 45% were considered refractory to their last therapy; 92% had received prior CHOP or CHOP-like regimens. Forty patients (67%) had completed 3 or more cycles of bendamustine; 25% received all 6 cycles of therapy. The ORR after 3 cycles of bendamustine was 50%, with CR (including CRu) in 28% of patients. The median duration of response was short at only 3.5 months. The ORR for AITL and PTCL-NOS was 69% and 41%, respectively (*P*=.47). However, this study was not powered to show differences in response rates between the different histologic subtypes.[52] The median PFS and OS for all patients were 3.6 and 6.3 months, respectively. The most common grade 3 or 4 toxicities included neutropenia (30%), thrombocytopenia (24%), and infectious events (20%).

Histone deacetylase (HDAC) inhibitors, including romidepsin and belinostat, have shown single-agent activity in patients with relapsed or refractory PTCL.[53–57] Romidepsin was approved by the FDA in June 2011 for the treatment of patients with relapsed PTCL based on the results of the pivotal multicenter phase II study that evaluated romidepsin in 130 patients with relapsed/refractory PTCL (PTCL-NOS, n=69 [53%]; AITL, n=27 [21%]; ALK-negative ALCL, n=21 [16%]).[54] Patients had received a median of 2 prior systemic therapies (range, 1–8), and prior autologous HSCT failed in 16%. Updated results from this study confirmed that responses were durable across all 3 subtypes of PTCL.[55] At a median follow-up of 22.3 months, there were no significant differences in ORR or rates of CR/CRu between the 3 most common subtypes of PTCL. The ORR was 29%, 30%, and 24%, respectively, for patients with PTCL-NOS, AITL, and ALK-negative ALCL. The corresponding rates of CR/CRu were 14%, 19%, and 19%, respectively. The median PFS was 20 months for all responders and it was significantly longer for patients who achieved CR/CRu for 12 months or more compared with those who achieved CR/CRu for less than 12 months or PR (29, 13, and 7 months, respectively). The median OS was not reached for patients who achieved CR/CRu and was 18 months for those who were in PR.[55] The most common grade 3 or greater adverse events included thrombocytopenia (24%), neutropenia (20%), and infections (19% for any; including pneumonia [5%] and sepsis [5%]).[54] The BELIEF trial evaluated belinostat in 129 patients with relapsed or refractory PTCL (pretreated with >1 prior systemic therapy).[57] The ORR in 120 evaluable patients was 25.8% (CR rate of 10.8% and PR rate of 15%). The median duration of response, median PFS, and median OS were 13.6, 1.6, and 7.9 months, respectively. The 1-year PFS rate was 19.3%.[57] The ORR was higher for AITL compared with other subtypes (45.5% vs 23.3% and 15.3%, respectively, for patients with PTCL-NOS and ALK-negative ALCL). Anemia (10.8%), thrombocytopenia (7%), dyspnea (6.2%), and neutropenia (6.2%) were the most common grade 3 or 4 adverse events. Belinostat was approved by the FDA in July 2014 for the treatment of relapsed or refractory PTCL.

Brentuximab vedotin is an antibody-drug conjugate that targets CD30-expressing malignant cells by binding to CD30 on the cell surface. The safety and efficacy of brentuximab vedotin (1.8 mg/kg intravenously every 3 weeks, up to 16 cycles) in patients with relapsed or refractory systemic ALCL was established in a multicenter phase II study (n=58). Patients had received a median of 2 prior systemic therapies (range, 1–6) and 62% were considered to have primary refractory disease; in addition, 50% of patients were refractory to their most recent prior therapy and 22% had never responded to any therapy.[58] In August 2011, based on the results from this study, brentuximab vedotin was approved by the FDA for the treatment of patients with systemic ALCL after failure of at least one prior multiagent chemotherapy regimen. Long-term follow-up results confirmed the durability of clinical benefit of brentuximab vedotin in patients with relapsed or refractory systemic ALCL.[59] After a median follow-up of approximately 4 years, the ORR of 83% (62% CR rate) was similar to the previously reported ORR of 86% (59% CR) evaluated by an independent review committee. The estimated 4-year survival rate was 64%. The median duration of objective response for all patients was 13.2 months (the median duration

of response for patients with a CR was 26.3 months). The planned subset analysis of a phase II multicenter study that evaluated the efficacy and safety of brentuximab vedotin in relapsed/refractory CD30-positive NHL showed that it was also effective in other subtypes of relapsed PTCL, particularly AITL.[60] 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%, 7.6 months, and 2.6 months, respectively. The ORR (54% vs 33%) and the median PFS (6.7 vs 1.6 months) were better for patients with AITL than those with PTCL-NOS.[60]

NCCN Recommendations

Participation in a clinical trial is strongly preferred for patients with relapsed/refractory disease. In the absence of a suitable clinical trial, the initial treatment for relapse/refractory disease depends largely on the patient's eligibility for transplant. Second-line systemic therapy followed by consolidation with HDT/ASCR or allogeneic SCT for those with a CR or PR is recommended for patients who are candidates for transplant. Localized relapse (limited to 1 or 2 sites) may be treated with involved-site RT before or after HDT/ASCR. Allogeneic SCT, when feasible, should be considered as a more reliably curative therapy for most patients with relapsed/refractory disease. HDT/ASCR may be an appropriate option for patients, particularly those with ALCL and for selected patients with other subtypes with chemosensitive relapsed disease. Patients who are not candidates for transplant should be treated with second-line systemic therapy or palliative radiotherapy.

Selection of Second-Line Systemic Therapy

Brentuximab vedotin should be the preferred choice of second-line therapy for relapsed/refractory ALCL.[58–60] Belinostat induced responses across all types of PTCL (with the exception of ALK-positive ALCL) and response rates were significantly higher for AITL than for other subtypes.[57] Bendamustine also induced higher response rates in patients with AITL compared with those with other subtypes.[52] Pralatrexate has very limited activity in AITL compared with other subtypes.[51] However, the aforementioned studies were not sufficiently powered to evaluate the response rates in specific subtypes.[51,52,57] Cyclosporine has been shown to be an effective treatment option for relapsed or refractory AITL.[48,49]

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

Summary

The poor results with conventional chemotherapy regimens led to the development of novel targeted therapies, resulting in improved clinical outcomes in patients with relapsed/refractory disease across many PTCL subtypes. The selection of appropriate treatment strategy for relapsed or refractory PTCL should be based on the patient's age, performance status, and eligibility for transplant; the agent's side effect profile; and the goals of therapy. Second-line systemic therapy followed by consolidation therapy with HDT/ASCR or allogeneic HSCT is recommended for patients who are candidates for transplant. Patients who are not candidates for transplant should

be treated with second-line systemic therapy or palliative radiotherapy.

References

1. Savage KJ. Peripheral T-cell lymphomas. Blood Rev 2007;21:201–216.
2. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 1997;89:3909–3918.
3. Vose J, Armitage J, Weisenburger D. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol 2008;26:4124–4130.
4. Parrilla Castellar ER, Jaffe ES, Said JW, et al. ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes. Blood 2014;124:1473–1480.
5. Iqbal J, Wright G, Wang C, et al. Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma. Blood 2014;123:2915–2923.
6. de Jong D, Vasmel WL, de Boer JP, et al. Anaplastic large-cell lymphoma in women with breast implants. JAMA 2008;300:2030–2035.
7. Roden AC, Macon WR, Keeney GL, et al. Seroma-associated primary anaplastic large-cell lymphoma adjacent to breast implants: an indolent T-cell lymphoproliferative disorder. Mod Pathol 2008;21:455–463.
8. Carty MJ, Pribaz JJ, Antin JH, et al. A patient death attributable to implant-related primary anaplastic large cell lymphoma of the breast. Plast Reconstr Surg 2011;128:112e–118e.
9. Lazzeri D, Agostini T, Bocci G, et al. ALK-1-negative anaplastic large cell lymphoma associated with breast implants: a new clinical entity. Clin Breast Cancer 2011;11:283–296.
10. Popplewell L, Thomas SH, Huang Q, et al. Primary anaplastic large-cell lymphoma associated with breast implants. Leuk Lymphoma 2011;52:1481–1487.
11. Miranda RN, Aladily TN, Prince HM, et al. Breast implant-associated anaplastic large-cell lymphoma: long-term follow-up of 60 patients. J Clin Oncol 2014;32:114–120.
12. Brody GS, Deapen D, Taylor CR, et al. Anaplastic large cell lymphoma occurring in women with breast implants: analysis of 173 cases. Plast Reconstr Surg 2015;135:695–705.
13. Gisselbrecht C, Gaulard P, Lepage E, et al. Prognostic significance of T-cell phenotype in aggressive non-Hodgkin's lymphomas. Groupe d'Etudes des Lymphomes de l'Adulte (GELA). Blood 1998;92:76–82.
14. Gascoyne RD, Aoun P, Wu D, et al. Prognostic significance of anaplastic lymphoma kinase (ALK) protein expression in adults with anaplastic large cell lymphoma. Blood 1999;93:3913–3921.
15. 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.
16. Mourad N, Mounier N, Briere J, et al. Clinical, biologic, and pathologic features in 157 patients with angioimmunoblastic T-cell lymphoma treated within the Groupe d'Etude des Lymphomes de l'Adulte (GELA) trials. Blood 2008;111:4463–4470.
17. Savage KJ, Harris NL, Vose JM, et al. ALK- anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. Blood 2008;111:5496–5504.
18. Pfreundschuh M, Trumper L, Kloess M, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: results of the NHL-B1 trial of the DSHNHL. Blood 2004;104:626–633.
19. 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.
20. 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.
21. Dunleavy K, Pittaluga S, Shovlin M, et al. Phase II trial of dose-adjusted EPOCH in untreated systemic anaplastic large cell lymphoma. Haematologica 2016;101:e27–29.
22. Reimer P, Rudiger T, Geissinger E, et al. Autologous stem-cell transplantation as first-line therapy in peripheral T-cell lymphomas: results of a prospective multicenter study. J Clin Oncol 2009;27:106–113.
23. d'Amore F, Relander T, Lauritzsen GF, et al. Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. J Clin Oncol 2012;30:3093–3099.
24. Moskowitz AJ, Lunning MA, Horwitz SM. How I treat the peripheral T-cell lymphomas. Blood 2014;123:2636–2644.
25. Song KW, Mollee P, Keating A, Crump M. Autologous stem cell transplant for relapsed and refractory peripheral T-cell lymphoma: variable outcome according to pathological subtype. Br J Haematol 2003;120:978–985.
26. Rodriguez J, Caballero MD, Gutierrez A, et al. High-dose chemotherapy and autologous stem cell transplantation in peripheral T-cell lymphoma: the GEL-TAMO experience. Ann Oncol 2003;14:1768–1775.
27. Kewalramani T, Zelenetz AD, Teruya-Feldstein J, et al. Autologous transplantation for relapsed or primary refractory peripheral T-cell lymphoma. Br J Haematol 2006;134:202–207.
28. Rodriguez J, Conde E, Gutierrez A, et al. The adjusted International Prognostic Index and beta-2-microglobulin predict the outcome after autologous stem cell transplantation in relapsing/refractory peripheral T-cell lymphoma. Haematologica 2007;92:1067–1074.
29. Chen AI, McMillan A, Negrin RS, et al. Long-term results of autologous hematopoietic cell transplantation for peripheral T cell lymphoma: the Stanford experience. Biol Blood Marrow Transplant 2008;14:741–747.
30. Corradini P, Dodero A, Zallio F, et al. Graft-versus-lymphoma effect in relapsed peripheral T-cell non-Hodgkin's lymphomas after reduced-intensity conditioning followed by allogeneic transplantation of hematopoietic cells. J Clin Oncol 2004;22:2172–2176.
31. Le Gouill S, Milpied N, Buzyn A, et al. Graft-versus-lymphoma effect for aggressive T-cell lymphomas in adults: a study by the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire. J Clin Oncol 2008;26:2264–2271.
32. Kyriakou C, Canals C, Finke J, et al. Allogeneic stem cell transplantation is able to induce long-term remissions in angioimmunoblastic T-cell lymphoma: a retrospective study from the lymphoma working party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 2009;27:3951–3958.
33. Dodero A, Spina F, Narni F, et al. Allogeneic transplantation following a reduced-intensity conditioning regimen in relapsed/refractory peripheral T-cell lymphomas: long-term remissions and response to donor lymphocyte infusions support the role of a graft-versus-lymphoma effect. Leukemia 2012;26:520–526.
34. Smith SM, Burns LJ, van Besien K, et al. Hematopoietic cell transplantation for systemic mature T-cell non-Hodgkin lymphoma. J Clin Oncol 2013;31:3100–3109.
35. Beitinjaneh A, Saliba RM, Medeiros LJ, et al. Comparison of survival in patients with T cell lymphoma after autologous and allogeneic stem cell transplantation as a frontline strategy or in relapsed disease. Biol Blood Marrow Transplant 2015;21:855–859.
36. Greer JP. Therapy of peripheral T/NK neoplasms. Hematology Am Soc Hematol Educ Program 2006:331–337.
37. Horwitz SM. Management of peripheral T-cell non-Hodgkin's lymphoma. Curr Opin Oncol 2007;19:438–443.
38. 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.
39. Connors JM, Sehn LH, Villa D, et al. Gemcitabine, dexamethasone, and cisplatin (GDP) as secondary chemotherapy in relapsed/refractory peripheral T-cell lymphoma. Blood 2013;122:4345–4345.
40. 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.
41. 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.
42. 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.
43. Zinzani PL, Alinari L, Tani M, et al. Preliminary observations of a phase II study of reduced-dose alemtuzumab treatment in patients with pretreated T-cell lymphoma. Haematologica 2005;90:702–703.

Non-Hodgkin's Lymphomas, Version 3.2016

44. 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.

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

46. 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.

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

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

49. 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.

50. O'Connor OA, Horwitz S, Hamlin P, et al. Phase II-I-II study of two different doses and schedules of pralatrexate, a high-affinity substrate for the reduced folate carrier, in patients with relapsed or refractory lymphoma reveals marked activity in T-cell malignancies. J Clin Oncol 2009;27:4357–4364.

51. 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.

52. 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.

53. Piekarz RL, Frye R, Prince HM, et al. Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma. Blood 2011;117:5827–5834.

54. 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.

55. 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.

56. Foss F, Advani R, Duvic M, et al. A phase II trial of belinostat (PXD101) in patients with relapsed or refractory peripheral or cutaneous T-cell lymphoma. Br J Haematol 2015;168:811–819.

57. 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.

58. 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.

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

60. 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.

Instructions for Completion

To participate in this journal CE activity: 1) review the learning objectives and author disclosures; 2) study the education content; 3) take the posttest with a 66% minimum passing score and complete the evaluation at **http://education.nccn.org/node/79463;** and 4) view/print certificate. After reading the article, you should be able to answer the following multiple-choice questions. Credit cannot be obtained for tests completed on paper. You must be a registered user on NCCN.org. If you are not registered on NCCN.org, click on "New Member? Sign up here" link on the left hand side of the Web site to register. Only one answer is correct for each question. Once you successfully answer all posttest questions you will be able to view and/or print your certificate. Software requirements: Internet

Posttest Questions

1. A 59-year-old man presents to his primary care physician with diffuse abdominal pain. He was previously treated with anthracycline-based chemotherapy, followed by HDT, followed by ASCR for ALK-1–negative ALCL. A CT scan of abdomen/pelvis shows a mesenteric mass, and a core biopsy confirms recurrent ALCL. What is the appropriate option for second-line therapy?
   a. Gemcitabine and oxaliplatin
   b. Involved-site radiation therapy
   c. Brentuximab vedotin
   d. Ifosfamide, carboplatin, and etoposide (ICE)
2. Which of the following single agents induces higher response rates in patients with angioimmunoblastic T-cell lymphoma than in those with other subtypes of PTCL?
   a. Pralatrexate
   b. Belinostat
   c. Romidepsin
   d. None of the above
3. True or False: Allogeneic SCT should be considered a more reliable curative therapy for most transplant-eligible patients with relapsed/refractory disease.