

# NCCN Guidelines® Insights

## Non-Hodgkin's Lymphomas, Version 3.2016

### Featured Updates to the NCCN Guidelines

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#### 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.

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## Non-Hodgkin's Lymphomas, Version 3.2016

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**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

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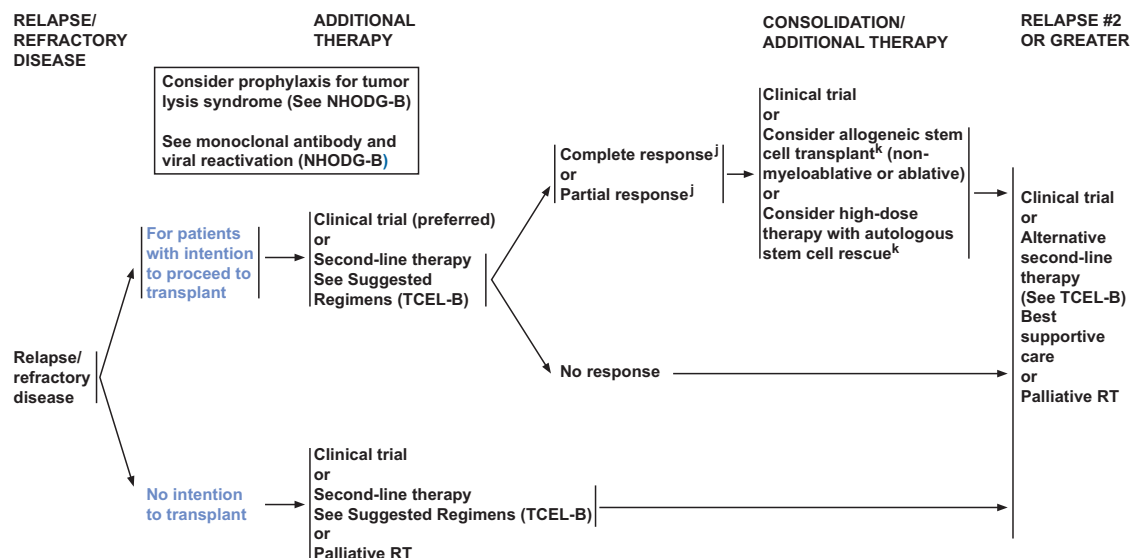
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<sup>j</sup>See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).  
<sup>k</sup>Localized areas can be irradiated before or after high-dose therapy.

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## 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.<sup>1</sup> PTCLs represent a relatively uncommon group of hematologic malignancies within non-Hodgkin's lymphomas (NHLs) and account for approximately 10% of all NHL cases.<sup>2</sup> 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%).<sup>3</sup> 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).<sup>4,5</sup> Breast implant-associated

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SUGGESTED TREATMENT REGIMENS FOR PTCL-NOS AND EATL<sup>a</sup>**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)<sup>d</sup>

**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<sup>e</sup> (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)

<sup>a</sup>See references for regimens TCEL-B 5 of 5.

<sup>d</sup>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.

<sup>e</sup>Activity has been demonstrated in small clinical trials and additional larger trials are needed.

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ALCL has also been recently reported to be a distinct entity from systemic ALCL.<sup>6–12</sup>

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.<sup>13–17</sup> 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.<sup>15,17</sup> 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.<sup>18–21</sup> 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.<sup>22,23</sup> 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.<sup>24</sup>

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

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## SUGGESTED TREATMENT REGIMENS FOR AITL<sup>a</sup>

### 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<sup>f</sup>

### 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<sup>g</sup> (category 2B)
- Cyclosporine<sup>g</sup>
- Gemcitabine
- Lenalidomide
- Pralatrexate<sup>f</sup>
- 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)

<sup>a</sup>See references for regimens TCEL-B 5 of 5.

<sup>g</sup>Activity has been demonstrated in small clinical trials and additional larger trials are needed.

<sup>f</sup>In AITL, pralatrexate has limited activity.

<sup>g</sup>With close follow-up of renal function.

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## Management of Relapsed/Refractory PTCL

### Role of Transplant

HDT/ASCR in patients with relapsed or refractory PTCL-NOS been evaluated in several retrospective studies.<sup>25–29</sup> 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%;  $P=.41$ ).<sup>25</sup> 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;  $P=.007$ ).<sup>26</sup> 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.<sup>26</sup> 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.<sup>27–29</sup>

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.<sup>30–33</sup> In a phase II study, Corradini et al<sup>30</sup> investigated the role of RIC allogeneic SCT in patients with relapsed or refractory PTCL (N=17); estimated 3-year progression-free sur-

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SUGGESTED TREATMENT REGIMENS FOR ALCL<sup>a</sup>**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<sup>b</sup> (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)

<sup>a</sup>See references for regimens TCEL-B 5 of 5.

<sup>b</sup>Activity has been demonstrated in small clinical trials and additional larger trials are needed.

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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%.<sup>30</sup> 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.<sup>31</sup> 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.<sup>31</sup> 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  $\geq 2$  lines of therapy before transplantation).<sup>32</sup> 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

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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, Trümper L, Ziepert M, et al. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin's Lymphoma Study Group. *Blood* 2010;116:3418-3425.

**CHOP followed by IVE**

Sienawski M et al. Evaluation of entropathy-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;11:1573-882.

Peng YL, Huang HQ, Lin XB, et al. [Clinical outcomes of patients with peripheral T-cell lymphoma (PTCL) treated by EPOCH regimen]. *Ai Zhong* 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**

Enlied 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**

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**Brentuximab vedotin**

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**TCEL-B**  
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were 54% and 64%, respectively. These outcomes were not significantly different between conditioning regimens.<sup>32</sup> 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.<sup>33</sup> 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.<sup>33</sup>

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.<sup>34</sup> 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/

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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 ( $n=76$ ).<sup>35</sup> 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 reli-

able curative option for most patients with relapsed/refractory PTCL based on eligibility for transplant.<sup>30-33</sup>

### Second-Line Systemic Therapy

In prospective randomized studies, PTCLs have been included with aggressive B-cell lymphomas.<sup>36,37</sup> 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.<sup>38-41</sup> Aggressive second-line chemotherapy with ICE (ifosfamide, carboplatin, etoposide) followed by HDT/ASCR was evaluated in patients with relapsed/refractory PTCL.<sup>38</sup> 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%;  $P=.0005$ ).<sup>38</sup>

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.<sup>39</sup> 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



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PFS was 9.3 months.<sup>40</sup> 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%.<sup>41</sup>

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).<sup>42</sup> However, alemtuzumab was associated with significant hematologic toxicity and infectious complications, including 5 deaths due to opportunistic infections.<sup>42</sup> 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.<sup>43</sup> 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.<sup>42</sup>

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).<sup>44</sup> 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).<sup>45</sup> 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.<sup>46</sup> 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.<sup>47</sup> 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.<sup>48,49</sup> 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.<sup>48</sup> A more recent case report also demonstrated that cyclosporine is an effective treatment for AITL relapsing after HDT/ASCR.<sup>49</sup>

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.<sup>50,51</sup> 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).<sup>51</sup> 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).<sup>51</sup> The median duration of response was 10 months. For all patients, the median PFS and OS were 3.5 and 14.5 months, respec-

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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%).<sup>52</sup> 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.<sup>52</sup> 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.<sup>53–57</sup> 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%]).<sup>54</sup> 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.<sup>55</sup> 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.<sup>55</sup> 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%]).<sup>54</sup> The BELIEF trial evaluated belinostat in 129 patients with relapsed or refractory PTCL (pretreated with >1 prior systemic therapy).<sup>57</sup> 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%.<sup>57</sup> 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.<sup>58</sup> 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.<sup>59</sup> 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

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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.<sup>60</sup> 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.<sup>60</sup>

### 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.<sup>58-60</sup> 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.<sup>57</sup> Bendamustine also induced higher response rates in patients with AITL compared with those with other subtypes.<sup>52</sup> Pralatrexate has very limited activity in AITL compared with other subtypes.<sup>51</sup> However, the afore-

mentioned studies were not sufficiently powered to evaluate the response rates in specific subtypes.<sup>51,52,57</sup> Cyclosporine has been shown to be an effective treatment option for relapsed or refractory AITL.<sup>48,49</sup>

There are not enough data to support the use of a particular regimen for second-line therapy based on the subtype, with the exception of ALCL. 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

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

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### 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.

