Beyond the Guidelines in the Treatment of Peripheral T-Cell Lymphoma: New Drug Development

Andy I. Chen, MD, PhD, and Ranjana H. Advani, MD, Stanford, California

Peripheral T-cell lymphoma. Results using antimetabolites, immunotherapies, and histone deacetylase inhibitors have been particularly encouraging. These novel therapies are being tested as single agents and in combination with conventional lymphoma regimens in the frontline and salvage settings. Because of the rarity and heterogeneity of PTCL, national and international cooperation is needed to conduct the clinical studies required for the development of more effective treatment paradigms. These efforts are ongoing and will hopefully guide new strategies to improve the historically poor outcome of PTCL. (JNCCN 2008;6:428–435)

Key Words
Peripheral T-cell lymphoma, targeted therapy, antimetabolites, immunotherapy, histone deacetylase inhibitor

Abstract
Peripheral T-cell lymphomas (PTCLs) are a rare and diverse group of neoplasms with a poor prognosis. Management of these disorders has been largely extrapolated from the treatment of aggressive B-cell lymphomas; however, therapeutic responses to this approach are neither adequate nor durable for most patients with PTCL. Given the rarity of PTCL, much of the literature consists of studies with small sample size and anecdotal case reports. Therefore, no consensus exists on the best therapeutic strategy for either newly diagnosed or relapsed/refractory PTCL. This article reviews promising novel approaches in the treatment of PTCL and its subtypes. Investigation into the pathogenesis of PTCL has also identified new targets for treatment. These emerging therapies include new uses of existing agents and the development of novel agents specifically targeted against T-cell lymphoma.

Learning Objectives
Upon completion of this activity, participants will be able to:
- Describe the most common types of peripheral T-cell lymphomas (PTCLs) in North America
- Describe the 5-year disease-free survival rate for PTCLs
- Identify chemotherapy regimens currently used for the treatment of PTCLs
- Describe overall response rates associated with the use of immunotherapies for the treatment of PTCLs
- Describe response rates of PTCLs to different antimetabolites

Peripheral T cell lymphomas (PTCLs) are a rare and heterogeneous group of disorders with a poor prognosis whose optimal treatment is uncertain.
Organization classification recognizes 13 different types of mature T-cell neoplasms, grouped into leukemic, extranodal, and nodal types. Of these, cutaneous T-cell lymphoma (CTCL) and T-cell leukemias are clinically unique entities and will not be discussed in this article except as they relate to the development of therapies for PTCL. In North America, PTCL-unspecified (PTCL-U), systemic anaplastic large-cell lymphoma (ALCL), and angioimmunoblastic T-cell lymphoma (AITL) are the most common forms of PTCL, whereas nasal-type extranodal natural killer/T-cell lymphoma (nNK/T) is more frequent in the Far East. Except for patients with ALCL that expresses anaplastic lymphoma kinase (ALK), those with PTCL have a poor prognosis compared with patients with aggressive B-cell non-Hodgkin's lymphoma (NHL), with a 5-year disease-free survival of less than 30% in large series. The International Prognostic Index for aggressive NHL, the most frequently used clinical prognostic score, stratifies patients with PTCL. However, patients with PTCL are more likely to present with high-risk features, such as advanced stage and extranodal sites, and have a markedly worse survival compared with those who have aggressive B-cell NHL of similar risk. Another prognostic index specifically for PTCL-U (PIT) is based on age, performance status, lactate dehydrogenase, and bone marrow involvement. Modifying the PIT to incorporate proliferation seems to further stratify survival compared with the International Prognostic Index or unmodified PIT.

Little consensus exists on the optimal treatment for PTCL in either the frontline or relapsed/refractory settings. Although CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) is the most commonly used initial therapy, this approach is extrapolated from the treatment of aggressive B-cell NHL and is not adequate for PTCL, because most patients have refractory disease or experience relapse. In the International T-Cell Lymphoma Project, no difference in overall survival was seen between patients who did and who did not receive anthracyclines for PTCL. More aggressive combination chemotherapy regimens, such as hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine) and VIP-ABVD (etoposide, ifosfamide, cisplatin, doxorubicin, bleomycin, vincristine, dexamethasone), have not been shown to be superior to CHOP and were significantly more toxic. The additive benefit of autologous hematopoietic cell transplant (autoHCT) as first consolidation in PTCL is controversial, because a significant fraction of patients in prospective trials had disease that was refractory to induction therapy and did not undergo autoHCT. For relapsed/refractory disease, salvage combination chemotherapy followed by autoHCT is typically offered, but few patients experience a durable benefit from this approach. Allogeneic HCT is also being explored for relapsed/refractory PTCL, with encouraging results.

The NCCN guidelines for PTCL reflect this lack of conclusive data, and clinical trial participation is encouraged for all patients. Because of the limitations of current therapies, novel targeted strategies are being investigated in PTCL. Several new agents that have shown activity in CTCL and T-cell leukemias are being explored in PTCL, both alone and in combination with chemotherapy. This article focuses on promising new therapies for PTCL, grouped largely according to mechanism of action on specific targets or by emerging approaches for specific subtypes of PTCL (Table 1).

**Targeted Therapies**

**Immunotherapies**

Denileukin diftitox, a fusion protein between interleukin-2 (IL-2) and diphtheria toxin, is approved for use in CTCL and targets the intermediate- and high-affinity IL-2 receptors expressed on T cells. IL-2 is a potent growth factor for T cells that causes T-cell activation and proliferation. In a single-agent phase II study, 13 of 27 patients with relapsed/refractory PTCL had objective responses, including 6 complete responses. Several responses were seen in patients with tumors negative for CD25, the high-affinity receptor for IL-2. The combination of denileukin diftitox with CHOP as initial therapy for PTCL is being explored in an ongoing phase II trial, and interim results have shown 22 complete (including unconfirmed) and 6 partial responses in 31 evaluable patients, with a median response duration of 13 months. Despite its promise in PTCL, denileukin diftitox poses considerable challenges for development in combination therapies because of its significant toxicities, such as acute hypersensitivity, peripheral edema, and hypoalbuminemia.

Alemtuzumab is a humanized anti-CD52 antibody and causes profound depletion of CD52+ cells.
CD52 is a cell surface glycoprotein highly expressed on all lymphocytes, including T cells, B cells, and natural killer cells, and on monocytes and sperm. Although it was originally approved for B-cell chronic lymphocytic leukemia, overall response rates of 55% to 75% have been reported in CTCL and T-cell leukemias. In relapsed/refractory PTCL, responses have been reported with standard- and reduced-dose alemtuzumab. A recent Italian multicenter study that combined alemtuzumab with CHOP as initial therapy for PTCL reported an overall response rate of 75% in 24 patients, with 17 complete responses. However, the 1-year progression-free survival at a median follow-up of 16 months was only 54%. In addition, severe lymphopenia and neutropenia were common, and substantial infectious toxicities were observed despite prophylaxis. Other studies combining alemtuzumab with chemotherapy have also reported similar response rates and high toxicity.

CD2 and CD4 are both T-cell markers that are often expressed in PTCL. Zanolimumab is a humanized anti-CD4 antibody in clinical development that has shown significant activity in CTCL. In PTCL, interim results from an ongoing phase II study reported 2 unconfirmed complete responses and 3 partial responses in 21 patients with relapsed/refractory CD4+ PTCL. Siplizumab is a humanized anti-CD2 antibody also in clinical development. Interim results from a phase I study in CD2+ T-cell leukemia and lymphoma reported 1 complete response in 9 cases of PTCL. Another potential T-cell surface target is chemokine receptor 4 (CCR4), which is expressed by adult T-cell leukemia/lymphoma and a subset of PTCL. A humanized antibody to CCR4 (KW-0761) is currently undergoing early phase testing for CCR4+ adult T-cell leukemia/lymphoma and PTCL.

## Antimetabolites

Gemcitabine, a pyrimidine analogue similar to cytarabine, has significant activity in various solid tumors and lymphoid malignancies. Gemcitabine competes with the natural nucleotide deoxycytidine and inhibits DNA synthesis and ribonucleotide reductase. In patients with relapsed/refractory PTCL, single-agent

| Table 1 Trials of New Agents in the Treatment of Peripheral T-Cell Lymphoma |
|---------------------------------|-----------------|-----------------|-----------------|
| Mechanism                      | Agent (Reference) | N   | ORR (CR) % | Response Duration |
| Immunotherapy                  | Denileukin difftox    | 27  | 48 (22)   | 6 mo             |
|                                | Denileukin difftox + CHOP | 31  | 90 (71)   | 13 mo            |
|                                | Alemtuzumab           | 14  | 36 (21)   | 2-12 mo          |
|                                | Alemtuzumab (reduced dose) | 10  | 60 (20)   | 7 mo             |
|                                | Alemtuzumab + CHOP    | 24  | 75 (71)   | 11 mo            |
|                                | Zanolimumab           | 21  | 24 (9)    | 1-8 mo           |
|                                | Siplizumab            | 9   | 11 (11)   | NR               |
| Antimetabolite                 | Gemcitabine           | 13  | 69 (8)    | NR               |
|                                | Gemcitabine           | 10  | 60 (20)   | 13 mo            |
|                                | Pentostatin           | 5   | 80 (40)   | 4 mo             |
|                                | Pralatrexate          | 16  | 62 (56)   | NR               |
| HDAC                           | Romidepins            | 19  | 26 (10)   | 8-14 mo          |
|                                | Belinostat            | 11  | 18 (9)    | 3-4 mo           |
| AITL-specific                  | Cyclosporine          | 12  | 67 (25)   | 2-120 mo         |
|                                | Rituximab + CHOP      | 9   | 89 (89)   | 7-53 mo          |
| nNK/T-specific                 | Asparaginase          | 33  | 51 (51)   | 55% OS at 5 y    |
| ALCL-specific                  | SGN-30               | 39  | 20 (5)    | 1-12 mo          |
|                                | MDX-060              | 7   | 28 (28)   | 2-24 mo          |

*Frontline therapy. All other studies in relapsed/refractory. Response duration listed as median if available or range.

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CR, complete response rate; HDAC, histone deacetylase; nNK/T, natural killer/T-cell lymphoma; NR, not reported; ORR, overall response rate; OS, overall survival.
Belinostat
Romidepsin (depsipeptide), also a pan-HDAC inhibitor, has activity in CTCL. In an interim evaluation of an ongoing phase II trial in PTCL, 5 of 19 patients with relapsed/refractory disease responded to romidepsin, with 2 complete responses. Belinostat (PXD101) is another pan-HDAC inhibitor being tested in CTCL and PTCL. An interim analysis of a continuing phase II study reported 2 complete responses and 5 cases of stable disease in 11 patients with PTCL. A concern with pan-HDAC inhibitors is cardiac toxicity from QT prolongation, but the reported incidence in published trials is less than 5%. Selective HDAC inhibitors are also currently under development.

Other Agents

Bortezomib is the first approved proteasome inhibitor and has shown activity in various lymphomas. In a recent Italian study, 8 of 12 patients with relapsed/refractory CTCL responded to single-agent bortezomib with 2 complete responses. This agent is being evaluated in PTCL as a single agent and in combination with conventional chemotherapy.

Targeted kinase inhibitors are being explored in lymphoma, and many ongoing trials include PTCL. Inhibitors of protein kinase C, phosphatidyl-inositol-3-kinase, AKT, mTOR, cyclin-dependent kinases, aurora kinase, and various tyrosine kinases are currently in early phase trials. Syk, a receptor-associated tyrosine kinase, may be a particularly attractive target, because it was expressed in 94% of all PTCL tested in one series and is involved in a translocation found in a subset of PTCL-U. UCN-01 (hydroxystauroporine), an inhibitor of protein kinase C and cyclin-dependent kinases, is also an inhibitor of ALK and is being evaluated in ALCL.

Lenalidomide is an immunomodulatory and antiangiogenic agent approved for multiple myeloma and myelodysplastic syndrome. Lenalidomide inhibits production of angiogenic cytokines, activates apoptosis, alters cell adhesion, and stimulates lymphocyte function. Early phase studies have shown activity in relapsed/refractory aggressive B-cell NHL and CTCL, and this agent is currently undergoing testing in PTCL.

Therapies for Specific Subtypes of PTCL

Angioimmunoblastic T-Cell Lymphoma

AITL is a unique subtype of PTCL characterized by immune dysregulation, proliferation of high endothelial...
venules, and expansion of dendritic cell networks. Gene expression profiling has shown that the neoplastic T cells are derived from CD4+ follicular T-helper cells. The neoplastic T cells express CXCL13, a chemokine that recruits and activates B cells and dendritic cells. Many cases of AITL are associated with the Epstein Barr virus (EBV), and a concomitant B-cell clonal disorder is often present. Abnormal vascular proliferation is a hallmark of this entity, and vascular endothelial growth factor (VEGF) is frequently overexpressed in AITL. Although the exact pathogenesis of AITL is controversial, Dunleavy et al. proposed an interesting model incorporating multiple cellular interactions. In this model, EBV-positive B cells are believed to be the instigating cells that activate follicular helper T cells, resulting in chemokine induced B-cell activation, follicular dendritic cell expansion, and vascular proliferation. Given this complex interplay, therapies directed at T cells, B cells, EBV, and angiogenesis could all be of interest in AITL. Because of the number of interactions, an approach that simultaneously targets multiple abnormal pathways in AITL might be particularly effective.

Cyclosporine, an immunosuppressant that binds cyclophilin in T cells and inhibits T-cell activation, targets the immune dysregulation characteristic of AITL. Of 12 patients with relapsed/refractory AITL, 8 experienced responses, including 5 complete responses with single-agent cyclosporine. The therapy was durable in some cases and well tolerated, and is undergoing further testing in an ECOG trial.

Rituximab has been combined with CHOP in frontline therapy to target the B-cell component in AITL. Of 9 patients, 8 experienced a complete response; 5 had a monoclonal or oligoclonal B-cell population, which may have contributed to the high response rate. This concept is being explored further by the Goupe d’Eude des Lymphomes de l’Adulte in frontline therapy for AITL.

VEGF and VEGF receptor expression have been reported in AITL and other types of PTCL, with expression shown to be an independent prognostic marker associated with poor outcome. Case reports suggest that patients with AITL have experienced response to bevacizumab, an antibody that targets VEGF. The combination of bevacizumab with CHOP as frontline therapy for PTCL is being tested by the ECOG.

### Nasal-Type Extranodal NK/T-Cell Lymphoma

nNK/T is an EBV-associated PTCL that typically presents with sinonasal disease. Although limited-stage disease is generally treated with a combination of radiation and chemotherapy, advanced-stage and relapsed/refractory disease are notoriously difficult to manage. In vitro natural killer cells are particularly sensitive to asparagine depletion, and asparaginase treatment results in profound depletion of asparagine in vivo. Asparaginase, a key component of lymphoblastic lymphoma therapy, induced responses in relapsed/refractory nNK/T as a single agent and in combination with chemotherapy. An asparaginase-based regimen is being evaluated as up-front therapy for nNK/T in Asia in the SMILE (steroids, methotrexate, ifosfamide, L-asparaginase, etoposide) trial.

### Anaplastic Large-Cell Lymphoma

In contrast to ALK-positive ALCL, ALK-negative ALCL has a poor prognosis and is managed similarly to PTCL-U. ALCL typically expresses CD30, a tumor necrosis factor receptor family member, and several antibodies targeting this protein have been developed. A chimeric anti-CD30 antibody (SGN-30) showed single-agent efficacy in a multicenter phase II study of relapsed/refractory CD30+ ALCL. In this study, 8 of 39 patients with ALCL experienced response to SGN-30, including 2 with durable complete responses. In a phase I-II trial, a humanized anti-CD30 antibody (MDX-060) induced complete responses in 2 of 7 patients with relapsed ALCL. Both antibodies were well tolerated and are being evaluated in expanded trials.

### Conclusions

Currently, the optimal treatment for PTCL is uncertain. Although a minority of patients can be cured with conventional combination chemotherapy and stem cell transplantation, most eventually develop progressive disease. Many new agents, ranging from antimetabolites to targeted therapies, have shown encouraging responses, and several agents approved for other entities also have activity in PTCL. However, most reports have limited patient numbers and duration of follow-up. Investigation into the biology of PTCL has identified key features of specific forms of PTCL and revealed new avenues for therapy. These type-specific targets are leading to the development of
rational therapies for individual forms of PTCL. It is becoming clear that the various types of PTCL differ significantly in their pathogenesis and natural history, and optimal treatment will likely require a tailored approach to exploit the unique sensitivities of each type. Future progress in PTCL will require major collaborative efforts to evaluate novel agents and accrue patients to trials. These efforts are ongoing and will hopefully guide new treatment strategies to improve the historically poor outcome of PTCL.

References


Peripheral T-Cell Lymphomas (PTCLs) and New Treatment Drugs

To obtain credit, you should first read the journal article. After reading the article, you should be able to answer the following, related, multiple-choice questions. To complete the questions and earn continuing medical education (CME) credit, please go to [http://www.medscape.com/cme/jnccn](http://www.medscape.com/cme/jnccn).

Credit cannot be obtained for tests completed on paper, although you may use the worksheet below to keep a record of your answers. You must be a registered user on Medscape.com. If you are not registered on Medscape.com, please click on the New Users: Free Registration link on the left hand side of the website to register.

Only one answer is correct for each question. Once you successfully answer all post-test questions you will be able to view and/or print your certificate. For questions regarding the content of this activity, contact the accredited provider, CME@medscape.net. For technical assistance, contact CME@webmd.net.

American Medical Association’s Physician’s Recognition Award (AMA PRA) credits are accepted in the US as evidence of participation in CME activities. For further information on this award, please refer to [http://www.ama-assn.org/ama/pub/category/2922.html](http://www.ama-assn.org/ama/pub/category/2922.html). The AMA has determined that physicians not licensed in the US who participate in this CME activity are eligible for AMA PRA Category 1 Credits™. Through agreements that the AMA has made with agencies in some countries, AMA PRA credit is acceptable as evidence of participation in CME activities. If you are not licensed in the U.S. and want to obtain an AMA PRA CME credit, please complete the questions online, print the certificate and present it to your national medical association.

1. Which one of the following types of peripheral T-cell lymphomas (PTCLs) is least common in North America?
   A. PTCL unspecified
   B. Systemic anaplastic large-cell lymphoma
   C. Nasal-type extranodal natural killer/T-cell lymphoma
   D. Angioimmunoblastic T-cell lymphoma

2. The 5-year survival for patients with PTCL in large series is best described by which one of the following?
   A. 30%
   B. 40%
   C. 50%
   D. 60%

3. Which one of the following combination regimens is considered superior for the treatment of PTCLs?
   A. CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
   B. Hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine)
   C. VIP-ABVD (etoposide, ifosfamide, cisplatin, doxorubicin, bleomycin, vincristine, dexamethasone)
   D. None of the above

4. Which one of the following best describes the overall response rates associated with the use of alemtuzumab, an immunotherapy, for PTCLs and T-cell leukemias?
   A. 10% to 35%
   B. 40% to 50%
   C. 55% to 75%
   D. 80% to 95%

5. Which one of the following antimetabolites, used as a single agent, has been found to be associated with a response rate of 60% to 69% for PTCLs with a complete response rate of 8% to 20%?
   A. Gemcitabine
   B. Nelarabine
   C. Fludarabine
   D. Forodesine

Activity Evaluation

1. The activity supported the learning objectives.
   - Strongly Disagree 1 2 3 4 5
   - Strongly Agree

2. The material was organized clearly for learning to occur.
   - Strongly Disagree 1 2 3 4 5
   - Strongly Agree

3. The content learned from this activity will impact my practice.
   - Strongly Disagree 1 2 3 4 5
   - Strongly Agree

4. The activity was presented objectively and free of commercial bias.
   - Strongly Disagree 1 2 3 4 5
   - Strongly Agree