Clinical Roundtable Monograph

Clinical Advances in Hematology & Oncology November 2011

Peripheral T-Cell Lymphomas: Diagnosis and Treatment Options

Proceedings From a Live Roundtable, August 17, 2011, Kauai, Hawaii

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A CME Activity
Approved for
1.25 *AMA PRA*
Category 1 Credit(s)™

Release Date: November 2011
Expiration Date: November 30, 2012
Estimated time to complete activity: 1.25 hours
Project ID: 8400

Abstract: Peripheral T-cell lymphomas are a collection of rare diseases, most of which have a poor prognosis. The basic categories include precursor lymphoid neoplasms (eg, lymphoblastic lymphoma); mature natural killer/T-cell neoplasms and extranodal lymphomas, including enteropathy-associated T-cell lymphoma; hepatosplenic T-cell lymphoma; and subcutaneous panniculitis-like T-cell lymphoma. The most common varieties are the nodal types, which include peripheral T-cell lymphoma not otherwise specified, anaplastic large cell lymphomas, and angioimmunoblastic T-cell lymphomas. Each of the subtypes has characteristic clinical manifestations. The frequencies of the subtypes vary by geographic region. The diagnosis can be difficult, and the World Health Organization classification system was recently evaluated to assess its clinical applicability and reproducibility for peripheral T-cell lymphomas and natural killer/T-cell lymphomas. At least 10% of patients are incorrectly diagnosed by local laboratories, and many subtypes need better diagnostic markers and criteria. Currently, an increasing number of effective and tolerable therapies are becoming available, including pralatrexate, brentuximab vedotin, romidepsin, and bendamustine. Accurate diagnosis is necessary to allow appropriate treatment, as exemplified by patients with anaplastic large cell lymphoma that expresses high levels of CD30, who have high response rates to brentuximab vedotin. Patients with peripheral T-cell lymphoma should be enrolled in clinical trials when possible. New medications should be incorporated into therapies in well-designed clinical trials to develop appropriate safety and efficacy data.

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Supported through an educational grant from
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Target Audience

This activity has been designed to meet the educational needs of oncologists, hematologists, and other healthcare professionals involved in the management of patients with T-cell lymphoma.

Statement of Need/Program Overview

In the United States, there are approximately 66,000 new cases of non-Hodgkin lymphoma each year; peripheral T-cell lymphoma (PTCL) represents approximately 10–15% of these cases. Approximately 70% of PTCL patients present with stage III or IV disease, often with impaired performance status. Marked differences exist in the clinical features that relate to the survival of these patients, and problems exist with classification. Improved classifications should be based on specific cell types and molecular or genetic mechanisms, rather than on clinical features and clinical pathologic syndromes. The current recommendation for initial treatment of PTCL is to enroll the patient in a clinical trial because standard frontline therapies are suboptimal. The cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen is used in PTCL because it has been the standard therapy for aggressive B-cell lymphomas. Clinical data, however, make it hard to justify anthracycline as a part of initial treatment. Currently, an increasing number of effective and tolerable therapies are becoming available, including pralatrexate, brentuximab vedotin, romidepsin, and bendamustine.

Educational Objectives

After completing this activity, the participant should be better able to:

- Identify areas of diagnostic confusion in peripheral T-cell lymphomas
- Describe clinical data in the treatment of peripheral T-cell lymphomas
- Use evidence-based decision-making to select optimal treatment for patients with peripheral T-cell lymphomas
- Assess clinical data on emerging treatment strategies in patients with peripheral T-cell lymphomas
- Outline strategies for the integration of new agents into current clinical practice

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Introduction to Peripheral T-Cell Lymphomas

Bruce D. Cheson, MD

The classification schemes for lymphomas have evolved in the past 50 years.[1,2] Initially, the Rappaport classification simply made a distinction between Hodgkin and non-Hodgkin lymphoma[3]; Lukes and Collins modified this classification in 1974.[4] Also in 1974, the Kiel classification, which distinguished between B-cell and T-cell origin, was published.[5] In the 1980s, the National Cancer Institute (NCI) working formulation defined 3 grades of lymphoma. In 1994, important subtypes of B-cell and T-cell lymphomas were identified with the Revised European-American Lymphoma (REAL) classification.[6] This classification was further refined in the World Health Organization (WHO) classification currently in use.[7]

Classification of Aggressive T-Cell Lymphomas

The T-cell and natural killer/T-cell lymphomas (NK/TCL) are now recognized as having several distinct categories, which include precursor lymphoid neoplasms, such as T-lymphoblastic leukemias/lymphomas; mature NK/T-cell neoplasms, which are cutaneous, primarily mycosis fungoides; extranodal, such as NK/T-cell type; enteropathy-associated T-cell lymphoma; hepatosplenic T-cell lymphoma; and subcutaneous panniculitis-like T-cell lymphoma. The nodal types are the most common, and include peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), anaplastic large cell lymphomas, and angioimmunoblastic T-cell lymphomas (AITLs). The other subtypes occur in just a small percentage of patients. The leukemic versions include adult T-cell leukemia/lymphoma (ATLL), aggressive NK cell leukemias, and T-cell prolymphocytic leukemias.

Occurrence of T-Cell Lymphomas

The T-cell lymphomas are relatively uncommon. In the United States, there are approximately 66,000 new cases of non-Hodgkin lymphoma each year[8]; peripheral T-cell lymphoma (PTCL) represents approximately 10–15% of these cases.[9] Some estimates indicate that the incidence of PTCL is growing,[10] which may be driven by an aging population.

The incidence of the various histologies differs by geography.[11] For example, some areas of Japan with a high endemic rate of human T-lymphotropic virus type 1 (HTLV-1) have a much higher frequency of ATLL than Western countries. Other areas have a higher frequency of other histologies, such as NK/TCL, than Western countries.

Characteristics of Peripheral T-Cell Lymphomas

Patients with PTCL tend to present with unfavorable characteristics, such as advanced stage and high International Prognostic Index (IPI) scores.[12] PTCL is more common in men than women, and it tends to occur in patients who are older than 60 years. Approximately 70% of patients present with stage III or IV disease, often with impaired performance status. The majority of patients have both nodal and extranodal involvement. Patients with B-cell lymphomas tend to present more often with B symptoms, bone marrow involvement, skin lesions, and disseminated disease. The diagnosis can be quite difficult, and at least 10% of patients are incorrectly diagnosed by local laboratories. Therefore, a sample obtained via an excisional biopsy (not a fine needle aspirate) should be reviewed by an experienced hematopathologist.

Each of the T-cell lymphomas has characteristic clinical manifestations. For example, patients with the AITLs have diffuse lymphadenopathy, hepatosplenomegaly, and a skin rash.[13] Also, they can have hypergammaglobulinemia, autoimmune hemolytic anemia, fevers, and symptoms similar to those seen in vasculitis. The subcutaneous panniculitis-like T-cell lymphomas have skin panniculitis, with tender plaques or subcutaneous nodules.[14] The hepatosplenic type is characterized by hepatosplenomegaly, a history of immunosuppression, and a notable lack of lymphadenopathy.[15] These patients may have liver failure, a hemophagocytic syndrome, and fever of unknown origin. The NK/TCLs, particularly the nasal type, often present with chronic sinusitis, palatal ulcers, nasal swelling with facial pain, and orbital involvement, and are positive for the Epstein-Barr virus (EBV).[16]

The other T-cell lymphomas are also unique. ATLL, which is characterized by the HTLV-1 infection, has several clinical subtypes.[17] The smoldering type involves the skin with or without pulmonary infiltrates; involvement of other organs is rare. Patients tend to have normal lymphocyte counts, calcium levels, and lactate dehydro-

genase (LDH) levels. Patients with chronic ATLL have lymphocytosis involving the skin, lung, liver, and nodes; normal calcium levels; and LDH levels that are normal or only mildly elevated. Patients with acute ATLL generally have symptoms of leukemia, organomegaly, a high LDH level, hypercalcemia, and a rash. The lymphomatous variant involves organomegaly, lymphadenopathy, increased levels of LDH and calcium, and a few circulating cells known as flower cells.[18]

Prognosis for Peripheral T-Cell Lymphomas

Most PTCL subtypes have a worse prognosis than that seen in typical cases of diffuse large B-cell lymphoma.[12] The median overall survival for most PTCL subtypes is approximately 1–3 years, with a 5-year overall survival rate of only about 30%. The exception is patients with anaplastic large cell lymphomas that are positive for anaplastic lymphoma kinase (ALK), who have a 5-year survival rate of approximately 70% with standard cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) therapy. Patients with ALK-positive disease tend to fare much better than those with ALK-negative disease, but this outcome may reflect the fact that ALK-positive disease tends to occur in younger patients, and ALK-negative disease tends to occur in older patients.[19]

The IPI does not apply very well to patients with PTCL-NOS.[12] Patients with 1 or no risk factors have an excellent outcome of about 50% survival at 5 years or longer, but patients with 2 or more risk factors do relatively poorly. Gallamini and coworkers developed the Prognostic Index for PTCL unspecified (PIT) prognostic model, which uses age, performance status, LDH level, and bone marrow involvement to divide patients into groups with 0, 1, 2, 3, or 4 risk factors.[20] The PIT model discriminates better than the IPI with regard to prognosis. However, there is not yet any clinical validity to modifying therapy on the basis of the PIT score.

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The Importance of Accurate Diagnosis in T-Cell Lymphoma: A Pathologist's Perspective

Dennis D. Weisenburger, MD

The WHO classification of PTCL and NK/TCL was recently updated to include new categories and new diagnostic criteria,[1] although these criteria had not been formally evaluated. This classification is essentially a list of distinctive disease entities that include both actual diseases and syndromes. The WHO classification is based on morphology, immunophenotype, genetic abnormalities, and clinical features. The T-cell and NK-cell lymphomas are grouped together in the WHO classification because they are closely related biologically and share phenotypic and functional properties, such as cytotoxicity. The multiparameter approach of the WHO classification means that disease definition is sometimes heavily dependent upon the clinical features. This approach is due, in part, to the lack of specificity of other parameters and a lack of knowledge regarding molecular pathogenesis.

Frequency and Incidence of Non-Hodgkin Lymphoma Subtypes

The frequency of different non-Hodgkin lymphoma subtypes varies by region.[2] Different parts of the world have significant differences in the frequency of PTCL subtypes and NK/TCL. These conditions comprise about 9.5% of all non-Hodgkin lymphomas in North America and Europe, almost 16% in southern Africa, 13.5% in the Middle East, and more than 17% in the Far East.

The annual percent change in the incidence of lymphoid neoplasms from 1992–2001 was compared according to race and sex in the 12 Surveillance, Epidemiology, and End Results (SEER) registries in North America.[3] The incidence of B-cell lymphomas increased by only about 0.5% per year. However, across the whole group of T-cell and NK-cell neoplasms, the incidence increased almost 4% per year. The incidence of PTCL increased more than 6% per year. Another study reported that the incidence of PTCL has steadily increased from the early 1990s through 2005.[4] In comparison, the incidence of Hodgkin lymphoma has been decreasing slightly over time.[3]

International Study of Peripheral T-Cell and Natural Killer/T-Cell Lymphomas

Our international study of PTCL and NK/TCL reviewed 1,320 cases of these diseases.[2] The purpose of the study was to evaluate the WHO classification and assess its clinical applicability and reproducibility (Table 1). Patients had previously-untreated de novo PTCL or NK/TCL and were age 19 years or older. Patients were excluded if they had mycosis fungoides or Sézary syndrome. The patients presented between January 1, 1990, and December 31, 2002. The cases were consecutive and representative of the geographic region. Tissue biopsies adequate for diagnosis and classification were required, along with clinical data that included the clinical features, treatments, and follow-up information.

Pathology Review Process

The pathology review was conducted in 2 stages. First, an expert hematopathologist at 1 of 5 regional centers reviewed and classified all cases according to the WHO classification.[1] The phenotype was determined using available tissue blocks to perform a standard phenotype panel and, if indicated, cytogenetic and molecular studies were done. The local and regional phenotype data, along with any cytogenetic or molecular results, were tabulated for review. Then, the regional expert pathologist rendered the diagnosis and quantitated various pathologic parameters.

Table 1. Goals of the International Study of PTCL and NK/TCL[2]

- Evaluate the ability of hematopathologists to apply the WHO classification to a retrospective group of cases collected from sites around the world
- Determine the relative frequencies and geographic variations of the various lymphoma subtypes
- Evaluate the role of clinical data in diagnosing the various subtypes, which is an important part of the WHO classification
- Evaluate the prognostic value of pathologic factors such as the percentage of large or transformed tumor cells, Ki-67 proliferation, EBV status, and phenotypic markers
- Determine the intraobserver reproducibility and interobserver reproducibility of diagnoses for the various subtypes to determine how well pathologists can use the classification
- Determine the clinical correlations for the various lymphoma subtypes, including clinical features at presentation, and outcomes including treatment and survival

EBV=Epstein-Barr virus; PTCL=peripheral T-cell lymphoma; NK/TCL=natural killer/T-cell lymphoma; WHO=World Health Organization.

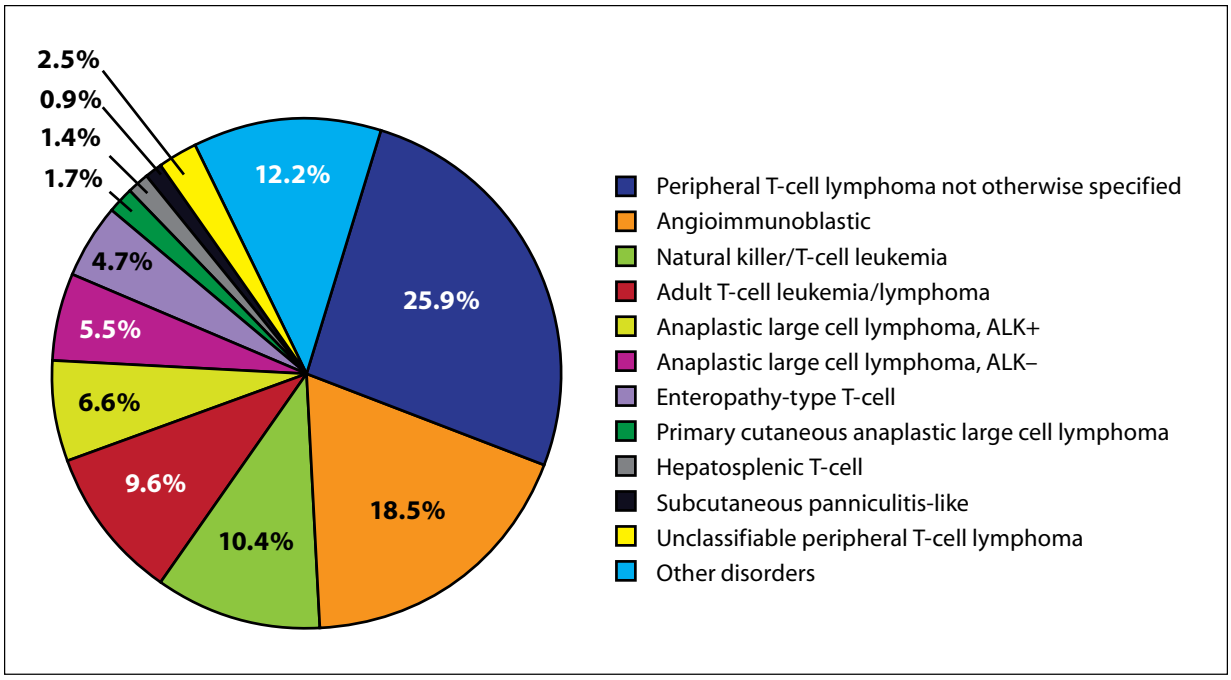

Figure 1. Subtypes of peripheral T-cell lymphoma identified in the International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study. ALK=anaplastic lymphoma kinase. Reprinted from the International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study: pathology findings and clinical outcomes. *J Clin Oncol.* 2008;26:4124-4130. Reprinted with permission © 2008 American Society of Clinical Oncology. All rights reserved.

In the second phase, 4 expert hematopathologists reviewed each case individually in 2 steps. First, they made a diagnosis based on the diagnostic slides and the immunostains, along with any available flow cytometry, cytogenetic, or molecular data. This diagnosis used minimal clinical data including only the age, sex, biopsy site, and site of the largest mass. The hematopathologists then made a second diagnosis after reviewing all of the pretreatment and follow-up clinical data. This second step determined if the more detailed clinical data would influence the diagnosis.

Afterward, a consensus diagnosis for each case was obtained when at least 3 of the 4 experts agreed on the second diagnosis. Any disagreements were settled in daily consensus conferences. The North American study site reviewed 25% of the cases, the European sites reviewed 34%, and the Far East site reviewed 41%.

Diagnoses

The most common subtype was PTCL-NOS, which was diagnosed in 25.9% of all the cases. The diagnosis was AITL in 18.5% of the cases, NK/TCL in 10.4%, and ATLL in 9.6%. Among the anaplastic large cell lymphomas, 6.6% were ALK-positive and 5.5% were ALK-negative. These were the most common lymphomas in the study. The less common lymphomas included the enteropathy type, which made up 4.7% of cases. The rest of the lymphomas made up 2% or less of the cases (Figure 1).[2]

A total of 12.2% of cases in this study were diagnosed as not being PTCL or NK/TCL. The diagnosis was wrong in 10.4% of the cases, and included diseases such as Hodgkin lymphoma (3%), B-cell lymphoma (1.4%), or a diagnosis other than lymphoma (2.3%).

Expert Agreement on Consensus Diagnoses

The experts' second diagnosis (made after reviewing all of the pretreatment and follow-up clinical data) agreed with the consensus diagnosis in more than 90% of the cases of ALK-positive anaplastic large cell lymphoma, ATLL, and NK/TCL. This high agreement is likely due to the specific diagnostic markers that facilitate a very accurate diagnosis for these conditions. For example, in ALK-positive anaplastic large cell lymphoma, the t(2;5) and staining for the ALK protein are highly sensitive and specific.[5] For ATLL, serology and molecular techniques allow the detection of HTLV-1 infection.[6] For NK/TCL, the clinical presentation is very distinctive and EBV is present in the tumor cells.[7]

The agreement rates were 80% or less for the other subtypes, which were AITL, enteropathy type, PTCL-NOS, panniculitis-like, hepatosplenic, ALK-negative anaplastic large cell lymphoma, and cutaneous anaplastic large cell lymphoma. This low rate of agreement

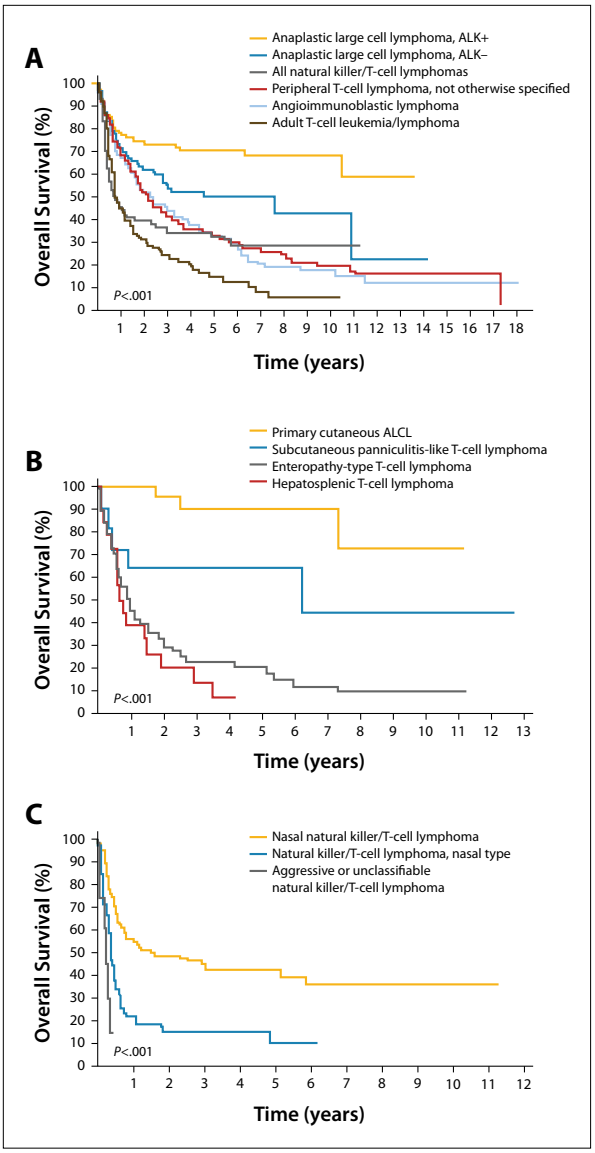

Figure 2. Overall survival according to subtype in the International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study. ALCL=anaplastic large cell lymphoma; ALK=anaplastic lymphoma kinase. Reprinted from the International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study: pathology findings and clinical outcomes. *J Clin Oncol.* 2008;26:4124-4130. Reprinted with permission

indicates the need for more specific markers and better diagnostic criteria for these entities.

After the regional experts re-reviewed a subset of the cases with the minimal clinical data, their diagnoses remained unchanged 81% of the time. This value varied among the 5 reviewers from 67–95%. This finding also reflects the lack of specific markers and precise criteria for the entities, which results in diagnoses that are less accurate than desired.

A total of 6.4% of the first diagnoses were changed to the consensus diagnosis after the second tier of review when all clinical data were included. The most common diagnostic change was from PTCL-NOS to ATLL, which made up almost 40% of the changed diagnoses; the addition of serology data for HTLV-1 allowed a more accurate diagnosis.

Subtype Frequencies

The frequencies of the subtypes vary by geography. The most common subtype in North America was PTCL-NOS, and AITL was most common in Europe. Anaplastic large cell lymphoma that is ALK-positive was more common in North America than in Europe or the Far East, whereas ALK-negative anaplastic large cell lymphoma was more common in Europe and very uncommon in the Far East. NK/TCL and ATLL made up more than 20% of the cases in the Far East, a much higher proportion than in North America or Europe.

Among the less common subtypes, the enteropathy type was most common in Europe, particularly in northern Europe where the frequency of celiac disease is also high. Among the other entities, hepatosplenic T-cell lymphoma was very uncommon in the Far East. Cutaneous anaplastic large cell lymphoma was more common in North America than in Europe, likely because in Europe these patients are seen by dermatopathologists and were not included in the study. Cutaneous anaplastic large cell lymphoma appeared to be uncommon in the Far East.

Survival Curves

The survival curves show marked differences in survival among the 6 most common entities (Figure 2A).[2] Patients with anaplastic large cell lymphoma that is ALK-positive have an excellent overall survival, and the ALK-negative form has the next best survival. The worst survival is seen in patients with ATLL.

Among the less common entities (Figure 2B), primary cutaneous anaplastic large cell lymphoma has an excellent prognosis, and subcutaneous panniculitis-like T-cell lymphoma also has a good prognosis. These are likely to mostly be alpha-beta type cases. The prognosis is very poor for the enteropathy type and for the hepatosplenic type.

Among just the NK/TCLs (Figure 2C), the survival is markedly different. The prognosis is relatively good for cases that present in the nasal or upper aerodigestive tract, with a plateau in the survival curve suggesting that about 40% of the patients are cured. However, the extranasal cases and the aggressive or unclassifiable cases had a dismal overall survival.

More detailed clinicopathologic analyses for the common subtypes in the study have recently been published,[8-13] and have delineated important prognostic factors. For example, the International Prognostic Index and the number of trans-

formed tumor cells (>70%) were found to be independent predictors of survival in PTCL-NOS, and could be used to stratify these patients for novel and risk-adapted therapies.[11]

Conclusion

Marked differences exist in the clinical features and the survival of patients with PTCL and NK/TCL, and problems exist with classification of these entities. Hence, new strategies are needed to better understand these neoplasms. For example, new classifications or changes in the current classification should be based on real diseases and not on syndromes. Improved classification should be based on specific cell types and molecular or genetic mechanisms, rather than on clinical features or clinicopathologic syndromes. Any new studies should utilize fresh and frozen tissue to allow detailed immunophenotypic, cytogenetic, and molecular genetic studies, and should include examination of gene expression profiles and the use of comparative genomic hybridization arrays. This approach will allow us to better understand these entities and better define them. Finally, because these diseases are rare, any future studies will require an international consortium of researchers that includes clinicians and pathologists in order to obtain the necessary number of cases.

Acknowledgment

Dr. Weisenburger has received fees for non-CME services from Seattle Genetics. He has performed contracted research for Spectrum Pharmaceuticals.

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Standard Therapy for Peripheral T-Cell Lymphomas

Bruce D. Cheson, MD

The current recommendation for initial treatment of PTCL is to enroll the patient in a clinical trial because standard frontline therapies are suboptimal.[1] Regimens that have been tried include CHOP and cyclophosphamide, vincristine, doxorubicin, and dexamethasone (HyperCVAD), along with a number of others.[2] Most PTCL patients—with the exception of ALK-positive cases—do poorly.

The CHOP regimen is used in PTCL because it has been the standard therapy for aggressive B-cell lymphomas. It has also been used for follicular lymphoma and mantle cell lymphoma. However, clinical data, including a recent meta-analysis,[3] make it hard to justify anthracycline as a part of initial treatment. Regimens with and without an anthracycline have a very similar outcome. Nevertheless, instead of trying

to move beyond CHOP, CHOP has been used as the basis for a variety of therapies.

Gallamini and coworkers reported a high response rate when they added alemtuzumab to CHOP, although they also reported an increased risk of severe, life-threatening, and fatal opportunistic infections.[4] Other groups are looking at this combination using different dosages and schedules, and hopefully they will not encounter the same negative experience.

The German High-Grade Lymphoma Study Group evaluated CHOP with the addition of etoposide (CHOEP) in a large number of patients.[5] Most of the patients had anaplastic large cell lymphoma, PTCL-NOS, or AITL. They received 6–8 cycles of either CHOP or CHOEP at various doses and schedules. Because older patients had difficulty tolerating the CHOEP regimen, these investigators recommended that CHOP-21 remain the standard for that group. For younger patients ages 18–60 years, the etoposide-containing regimens appeared to have a better outcome. It should be noted that this trial was not randomized.

Autologous stem cell transplant has been used as frontline therapy.[6] However, a drawback to this approach is that most patients have advanced stage disease, plus many have bone marrow involvement. About 40–50% of patients are not suitable for transplant due to progressive disease, and an additional 20–30% progress after the transplant. Autologous stem cell transplant is not something to be entered into with a great deal of optimism.

Fortunately, a variety of new drugs are available or are in clinical trials to treat patients with relapsed and refractory PTCLs.[7] These include a number of agents that will be discussed in the next section, such as the antifol pralatrexate; the histone deacetylase inhibitors, such as romidepsin and vorinostat; the alkylating agents, such as bendamustine; the aurora kinase inhibitors; and, most recently, the drug-antibody conjugate brentuximab vedotin (SGN-35), which has a high level of efficacy and is limited to CD30-positive diseases, notably anaplastic large cell lymphoma.[8] Also, a number of monoclonal antibodies, including alemtuzumab, have efficacy.[9] Other studies involve the monoclonals KW-0761, which targets CCR4,[10] and zanolimumab, which targets CD4.

Recommendations for Integrating Current and Emerging Therapies Into Clinical Practice

Clearly, I am not an advocate of CHOP therapy for patients with PTCL. I am excited about the increasing number of effective and tolerable therapies, such as pralatrexate, romidepsin, bendamustine, the monoclonal antibody drug conjugates, and others. However, we need to combine these drugs in a rational fashion. One drug is not going to make a huge impact on the overall survival of these patients. However, preclinical data suggest that it is quite possible that these drugs might be additive or even synergistic.[11] Trials of doublet therapy, such as pralatrexate and romidepsin, are in development. Once a doublet has been shown to be highly effective and tolerable, I propose that it be compared directly to CHOP. The goals would be to eliminate CHOP from our armamentarium in T-cell lymphoma, and to replace CHOP with targeted therapies that would be more effective as we develop better approaches for patients in the relapsed setting.

Conclusion

The PTCLs are a heterogeneous group of diseases that are challenging to diagnose. The incidence appears to be growing. Except for the cases that are ALK-positive, the prognosis is relatively poor. Improved treatments are clearly needed. To make progress in these diseases, patients should be accrued to clinical trials to test novel therapeutic approaches.

Acknowledgment

Dr. Cheson is a consultant for Cephalon.

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Newer Treatment Options for Peripheral T-Cell Lymphomas

Steven M. Horwitz, MD

Many advances have recently occurred in treatment options for PTCLs. Most trials are examining either new drugs in the relapsed setting or combinations of new drugs. Meanwhile, some of the newer drugs are more rapidly advancing to the upfront setting. In 2009, pralatrexate became the first drug approved for PTCL.[1] This past summer, 2 more drugs were approved: romidepsin in June and brentuximab vedotin in August.[2,3] Brentuximab vedotin was approved specifically for anaplastic large cell lymphoma and Hodgkin lymphoma.

Recent Study Data

The PROPEL (Pralatrexate in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma) trial set a benchmark, with its study of pralatrexate in 109 evaluable patients who had relapsed or refractory PTCL.[4] The overall response rate was 29%, and the median duration of response was 10.1 months. The romidepsin trial included 131 patients with PTCL.[5,6] The objective response rate was 25%, the complete response rate was 15%, and the median duration of response was 17 months; 94% of complete responders have not progressed as of the study data cutoff date. Both pralatrexate and romidepsin are reasonable options in the study populations, where they were primarily third-line and fourth-line treatments. We would hope that the response would be even better if those drugs were used earlier in the course of treatment (although still in the relapse setting).

Brentuximab vedotin had very high responses in patients who were CD30-positive and in treated subjects limited to relapsed Hodgkin lymphoma or systemic anaplastic large cell lymphoma only.[3,7] This antibody-drug conjugate uses an antibody to target CD30 and conjugates the antibody to the antitubulin agent monomethyl auristatin E (MMAE). The CD30 antibody binds to the tumor cell and undergoes endocytosis, which allows the chemotherapy to penetrate the nucleus. In that specific population of systemic anaplastic large cell lymphoma patients, the large T-cell lymphomas always express CD30. The objective response rate among 58 patients in this phase II study was 86%, with 53% of patients achieving complete responses. This activity is really remarkable in that population. Since systemic anaplastic large cell lymphoma is only about 15–20% of all the T-cell lymphoma cases, this is a select patient population, but the response rates were nonetheless very high.

Preliminary data were presented this summer from a trial of bendamustine in patients with relapsed or refractory PTCL.[8] A total of 38 evaluable patients had an overall response rate of 47%, although the median duration of response was short, at 157 days. This finding suggests that bendamustine may have activity in these patients, and it represents another option to consider in the relapsed or refractory setting in patients who have exhausted the approved options or to include in future combination studies.

Combining Therapies

Newer combinations should allow us in the clinical trial setting to transition beyond the identification of additional single agents with activity in relapsed patients and try to identify regimens that will improve the prognosis for the majority. Currently, all the newly approved drugs are being studied in the upfront setting. A phase I study in systemic anaplastic large cell lymphoma is examining brentuximab vedotin given either sequentially before CHOP or in combination with modified CHOP.[9] This study is hopefully setting the stage for a new upfront regimen for that subset of patients, which, if well tolerated, may lead to a further randomized study in untreated systemic anaplastic large cell lymphoma. Similarly, romidepsin is being combined with CHOP in a phase I study being done in France by the Groupe d'Etude des Lymphomes de l'Adulte (GELA).[10] Again, if the results look promising, they could lead to a randomized study in the untreated setting.

Pralatrexate

The approach with pralatrexate has been slightly different. Despite the inadequacies of CHOP in terms of durable remissions, a significant number of PTCL patients reach partial or complete remission with CHOP, and a current international study is evaluating whether that remission can be maintained with pralatrexate.[11] Patients are randomized in a 2:1 ratio either to receive pralatrexate maintenance or to be observed. This study is currently open and accruing. A phase I/II study of pralatrexate in cutaneous T-cell lymphoma found an objective response rate of 45% in 18 patients receiving pralatrexate at 15 mg/m^2 for 3 of 4 weeks, which is a dose that is a little less than half the standard dose for aggressive T-cell lymphomas.[12] A current phase I study in patients with cutaneous T-cell lymphoma is combining pralatrexate with bexarotene, which is a retinoid commonly used for mycosis fungoides.[13]

Optimal Use of Emerging Treatments

Patients with relapsed disease benefit from emerging treatments because the number of options available is significantly increasing. Although none of these drugs work for everybody, more options mean a better chance that something will work for an individual patient. Most of the newer agents can be given in a continuous or extended fashion, so that if patients do respond, the duration of response can be maximized by keeping them on therapy. In the uniformly CD30-expressing systemic anaplastic large cell lymphoma, a very high percentage of those patients will respond to brentuximab vedotin. New studies are examining brentuximab vedotin in patients with other subtypes of lymphoma and with present, but varying, levels of CD30 expression.[14] The goal is to evaluate the level of CD30 expression needed for activity and identify if a threshold level exists. These studies will allow us to determine who will benefit from this drug.

For other drugs, such as pralatrexate, romidepsin, and newer therapies, we still lack markers or other ways to predict which patients are likely to respond. The pralatrexate data suggest that patients with AITL may not respond as well, as there was a non–statistically insignificant lower response rate in those with AITL in the PROPEL study.[4] Although that lower rate may be an accurate reflection of response, caution in interpreting these results is warranted. The early NCI study of romidepsin reported a lower response rate for AITL than for other subtypes,[15] but trials in larger registrational settings found that the response rate was similar across subtypes.[16] Current studies have too few patients of the individual subtypes to specifically determine which subtypes have a better or worse response.

Studies in Progress

Other interesting drugs include KW-0761, an antibody targeting CCR4. Many T-cells and many T-cell lymphomas express CCR4. A phase II study of KW-0761 in patients with HTLV-1–associated lymphoma from Japan found a 50% objective response rate in the 26 patients evaluable for efficacy.[17] The enrolled patients had relapsed CCR4-positive, aggressive subtypes of ATLL. Efforts are under way to develop a larger study with the goals of confirming the response rate in HTLV-1 lymphomas and of expanding the activity or seeking activity in more common types of T-cell lymphoma.

For patients with nasal NK/TCL, L-asparaginase may be practice-changing. Nasal NK/TCL occurs primarily in Asia and is an EBV-positive lymphoma that usually, although not always, presents in the nasopharynx. A few studies have looked at the activity of L-asparaginase in those patients.[18]

A novel chemotherapy regimen—steroids, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE)—has been developed in Japan.[19] It is a very intense combination regimen with response rates that are quite high in nasal NK/TCL. We have recently treated patients with this regimen and also found high responses. Therefore, SMILE appears to be a very active chemotherapy regimen for that disease. Identification of especially active chemotherapy agents has the potential to improve the prognosis in nasal NK/TCL. Another study in the United States for untreated patients with aggressive T-cell lymphomas incorporates pralatrexate in a different way into the upfront regimen: it takes a variation of CHOP and alternates it with pralatrexate.[11] This regimen is akin to such alternating regimens as HyperCVAD.

Adverse Events

Because 2 of the new drugs for T-cell lymphoma, pralatrexate and romidepsin, are used only for this condition, many doctors may not be familiar with the side effects. The primary side effect of pralatrexate has been mucositis, specifically oral stomatitis.[4] Patients receiving various doses of pralatrexate have developed mouth sores that are usually mild but occasionally severe. In early studies done at Memorial Sloan-Kettering Cancer Center, it appeared that premedication with folic acid and vitamin B_{12}—to optimize homocysteine and methylmalonic acid levels—correlated with a decrease in mucositis, particularly high-grade mucositis.[20] At the current dose of 30 mg/m^2, some patients will experience grade 3/4 mucositis. The best intervention is probably to hold the dose for a week; in most patients, mucositis will resolve during this time. The use of other specific interventions, such as leucovorin, ice chips, or mouth rinses, has been reported anecdotally, but no data suggest that this approach eliminates or significantly reduces the risk of mucositis.[21] In a patient with relatively mild disease, pralatrexate is sometimes started at a lower dose, such as 20 mg/m^2 given 3 of 4 weeks, and titrated up if no side effects are seen. This approach is partly based on a study of cutaneous T-cell lymphoma patients, in which the pralatrexate dose was reduced from 30 mg/m^2 to 10 mg/m^2.[22] Good rates of response were seen in doses as low as 15 mg/m^2 every 3 of 4 weeks. Below 15 mg/m^2 every 3 of 4 weeks, significant responses were not seen. In this study, the rates of mucositis were less than those in the larger PROPEL study, and there was very little grade 3/4 mucositis. The most common hematologic side effect of pralatrexate is thrombocytopenia, which usually resolves when the drug is held for a week.

Romidepsin has been reasonably well tolerated. There had been some older concerns that romidepsin can cause QT prolongation. In more recent studies of patients with cutaneous T-cell lymphoma and PTCL, there has been almost no grade 3 QT prolongation and an absence of grade 4 QT prolongation.[6] Original studies used higher doses of the drug, which probably led to an overestimation

of the rate of QT prolongation. In addition, there is a current awareness that many other drugs used in these patients, including antiemetics and antibiotics, could be additive in QT prolongation when given with a histone deacetylase inhibitor. In the more recent studies of romidepsin, which show almost no clinically significant QT prolongation, patients were counseled to avoid other QT–prolonging drugs, particularly antibiotics; their electrolytes were frequently checked; and normalization of potassium and magnesium was performed routinely throughout cycles of treatment. It appears that under those parameters—in which exposure to other QT-prolonging agents is minimized and electrolytes are repleted to their normal value—there is much less risk for QT prolongation. The main hematologic side effect of romidepsin is, again, thrombocytopenia. As with pralatrexate, if the drug is held for a week, the platelet counts will usually return to an adequate level.

In the phase II study by Pro and colleagues, brentuximab vedotin was associated with grade 3/4 neutropenia (21%), thrombocytopenia (14%), and peripheral sensory neuropathy (10%).[7] These adverse events were considered manageable.

Integrating Emerging Therapies Into Clinical Practice

This is a very exciting time, but in practice the excitement must be tempered and built upon with caution. Since T-cell lymphoma patients have often not done well with standard therapies like CHOP, doctors have a strong and understandable desire to try to incorporate these new medicines. The best way to do that is on clinical studies. In the laboratory, the combination of pralatrexate with gemcitabine looked very promising, but the phase I study found significantly increased toxicity and lack of added efficacy.[23] We must try to do better when we mix drugs together in the upfront setting, where patients are not cured at a high rate. As much as possible, drugs should be combined in the context of a well-designed clinical trial. Efforts should be made to enroll sufficient numbers of patients in trials so that we avoid combining drugs in an ad hoc manner without appropriate safety data.

Acknowledgment

Dr. Horwitz is a consultant for Allos Therapeutics, Celgene, Seattle Genetics, Merck, Quest Diagnostics, and Spectrum Pharmaceuticals.

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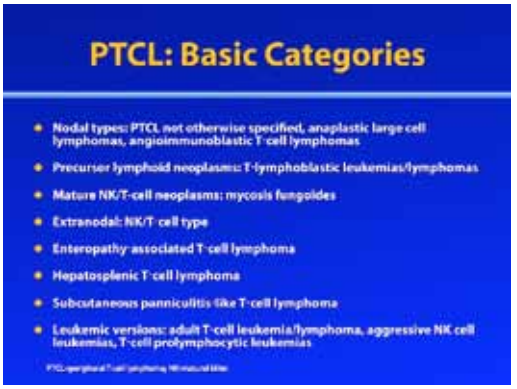

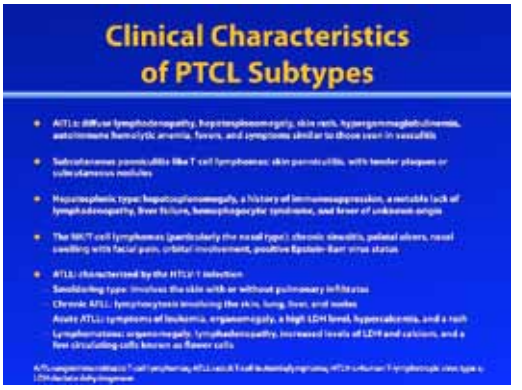

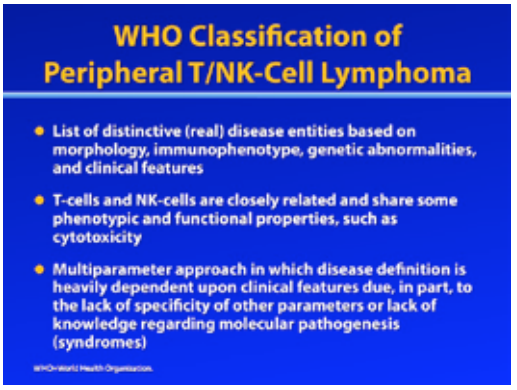

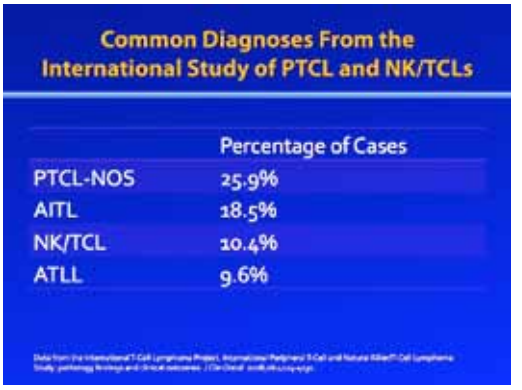

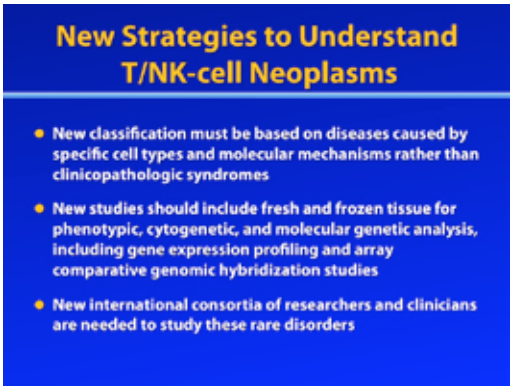

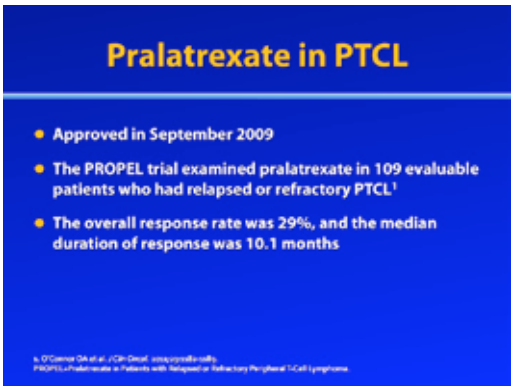

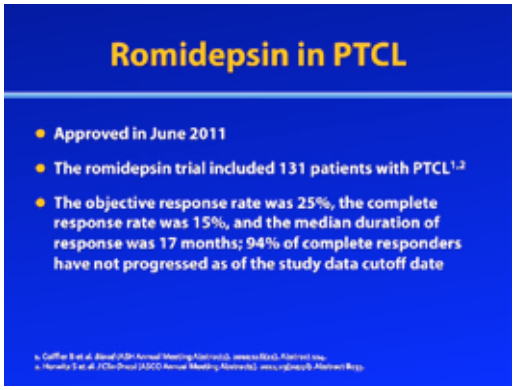

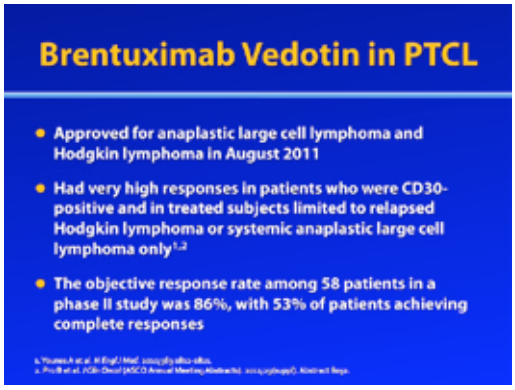

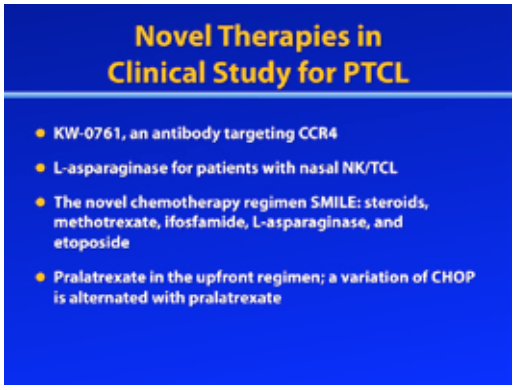

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Peripheral T-Cell Lymphomas: Diagnosis and Treatment Options

CME Post-Test: *Circle the correct answer for each question below.*

1. How many patients with peripheral T-cell lymphomas (PTCLs) present with stage III or IV disease?

   a. Approximately 40%
   b. Approximately 50%
   c. Approximately 60%
   d. Approximately 70%

2. How many PTCL patients are incorrectly diagnosed by local laboratories?

   a. Approximately 5%
   b. Approximately 10%
   c. Approximately 15%
   d. Approximately 20%

3. In the International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study, what percentage of the cases were diagnosed as angioimmunoblastic T-cell lymphomas?

   a. 9.6%
   b. 10.4%
   c. 18.5%
   d. 25.9%

4. In the International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study, which subtype had the worst survival?

   a. Adult T-cell leukemia/lymphoma
   b. Anaplastic large cell lymphoma
   c. Angioimmunoblastic T-cell lymphoma
   d. Peripheral T-cell lymphoma not otherwise specified

5. What is the current recommendation for initial treatment of PTCL?

   a. Autologous stem cell transplant
   b. Cyclophosphamide, doxorubicin, vincristine, and prednisone
   c. Cyclophosphamide, vincristine, doxorubicin, and dexamethasone
   d. Enrollment in a clinical trial

6. Which agent targets CD4?

   a. Bendamustine
   b. Pralatrexate
   c. Vorinostat
   d. Zanolimumab

7. What was the median duration of response in the PROPEL (Pralatrexate in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma) trial?

   a. 7.9 months
   b. 8.4 months
   c. 9.3 months
   d. 10.1 months

8. Which agent was shown to have an objective response rate of 86% in patients with relapsed/refractory systemic anaplastic large cell lymphoma?

   a. Alemtuzumab
   b. Bendamustine
   c. Brentuximab vedotin
   d. Romidepsin

9. A phase II study of KW-0761 in patients with human T-lymphotropic virus type 1–associated lymphoma from Japan found a ___ objective response rate in patients evaluable for efficacy.

   a. 20%
   b. 30%
   c. 40%
   d. 50%

10. The novel chemotherapy regimen SMILE (steroids, methotrexate, ifosfamide, L-asparaginase, and etoposide) has had a high response rate in patients with:

    a. Anaplastic large cell lymphomas
    b. Angioimmunoblastic T-cell lymphomas
    c. Hepatosplenic T-cell lymphoma
    d. Nasal natural killer/T-cell lymphomas

Evaluation Form: Peripheral T-Cell Lymphomas: Diagnosis and Treatment Options

PIM is committed to excellence in continuing education, and your opinions are critical to us in this effort. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Learning Objectives
After participating in this activity, I am now better able to:

1. Identify areas of diagnostic confusion in peripheral T-cell lymphomas	1	2	3	4	5
2. Describe clinical data in the treatment of peripheral T-cell lymphomas	1	2	3	4	5
3. Use evidence-based decision-making to select optimal treatment for patients with peripheral T-cell lymphomas	1	2	3	4	5
4. Assess clinical data on emerging treatment strategies in patients with peripheral T-cell lymphomas	1	2	3	4	5
5. Outline strategies for the integration of new agents into current clinical practice	1	2	3	4	5

Based upon your participation in this activity, choose the statement(s) that apply:
❒ I gained new strategies/skills/information that I can apply to my area of practice.
❒ I plan to implement new strategies/skills/information into my practice.
❒ I need more information before I can implement new strategies/skills/information into my practice behavior.
❒ This activity will not change my practice, as my current practice is consistent with the information presented.
❒ This activity will not change my practice, as I do not agree with the information presented.

What strategies/changes do you plan to implement into your practice? _____

_____

How confident are you that you will be able to make this change?
❒ Very confident ❒ Unsure
❒ Somewhat confident ❒ Not very confident

What barriers do you see to making a change in your practice? _____

_____

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

The content presented:

Enhanced my current knowledge base	1	2	3	4	5
Addressed my most pressing questions	1	2	3	4	5
Promoted improvements or quality in healthcare	1	2	3	4	5
Was scientifically rigorous and evidence-based	1	2	3	4	5
Avoided commercial bias or influence	1	2	3	4	5
Provided appropriate and effective opportunities for active learning (e.g., case studies, discussion, Q&A, etc)	1	2	3	4	5
My opportunity for learning assessment was appropriate to the activity	1	2	3	4	5

Handout materials were useful: ❒ Yes ❒ No ❒ No handouts for this activity

Would you be willing to participate in a post-activity follow-up survey? ❒ Yes ❒ No

Please list any clinical issues/problems within your scope of practice you would like to see addressed in future educational activities:

_____

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-tests by Course" and search by project ID 8400. Upon successfully registering/logging in and completing the post-test and evaluation, your certificate will be made available immediately.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

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For Physicians Only: I certify my actual time spent to complete this educational activity to be:
❒ I participated in the entire activity and claim 1.25 credits.
❒ I participated in only part of the activity and claim _____ credits.

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