Target Audience

This activity has been designed to meet the educational needs of oncologists, hematologists, and nurses involved in the management of patients with peripheral T-cell lymphoma (PTCL).

Statement of Need/Program Overview

Peripheral T-cell lymphomas (PTCL) are a heterogeneous group of malignancies that arise from mature T cells. PTCL accounts for approximately 10% of non-Hodgkin lymphoma cases. There are more than 20 different subtypes, the most common of which are PTCL not otherwise specified, angioimmunoblastic T-cell lymphoma, and anaplastic large-cell lymphoma. The characteristics of PTCL are distinct from those of B-cell lymphomas. Most PTCL subtypes are aggressive and treatment-resistant, and associated with a poor prognosis. PTCL is characteristically unresponsive to conventional chemotherapy. Newer agents, including antifolates, immunoconjugates, histone deacetylase inhibitors, monoclonal antibodies, nucleoside analogs, proteasome inhibitors, and signaling inhibitors, have improved outcomes for patients with relapsed/refractory PTCL. Four therapies recently gained approval from the US Food and Drug Administration for relapsed/refractory PTCL: pralatrexate, romidepsin, belinostat, and brentuximab vedotin (specifically for systemic anaplastic large-cell lymphoma). Use of these agents is supported by well-designed phase 2 trials. Autologous or allogeneic stem cell transplants are also options in the relapsed/refractory setting. Ongoing research is evaluating the use of new agents in the frontline setting and attempting to identify biological markers that predict treatment response.

Educational Objectives

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

- Discuss the diagnosis and classification of the various PTCL subtypes
- Compare the characteristics of PTCL subtypes, including aggressiveness and prognosis of the disease
- Employ treatment options for the frontline and salvage therapy of PTCL by subtype
- Discuss results reported from clinical trials evaluating new agents and strategies in the treatment of PTCL

Accreditation Statement

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There are no fees for participating in and receiving CME credit for this activity. During the period July 2015 through July 31, 2016, participants must 1) read the learning objectives and faculty disclosures; 2) study the educational activity; 3) complete the post-test by recording the best answer to each question in the answer key on the evaluation form; and 4) complete the evaluation form. You may complete the post-test and evaluation form online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-test/Evaluation by Course" and search by course ID 10866. Upon registering and successfully completing the post-test with a score of 75% or better and submitting the activity evaluation, your certificate will be made available immediately. Processing credit requests online will reduce the amount of paper used by nearly 100,000 sheets per year.

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Media

Interview

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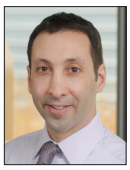
CLINICAL UPDATE

Current Developments in the Management of Lymphoma

Current and Novel Treatment Options for Peripheral T-Cell Lymphoma



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H&O What is peripheral T-cell lymphoma (PTCL)?

SH The term PTCL describes a group of more than 20 subtypes of non-Hodgkin lymphoma. These subtypes account for approximately 10% of non-Hodgkin lymphoma cases in the United States and Europe, and up to 24% in Asia.[1] PTCLs are cancers of mature or postthymic T cells. Most patients with PTCL have systemic disease. The systemic forms of these lymphomas are often aggressive, meaning that they grow relatively quickly. Treatment usually consists of combination chemotherapy given with curative intent.

The diagnosis requires a tissue biopsy with immunophenotyping to confirm that the malignant cells are T cells. The pathologist then identifies a subtype, which may require clinical and pathologic correlation. This is particularly true in the extranodal subtypes. The most common subtype is PTCL not otherwise specified (NOS); this subtype is used when the disease does not fit into any of the other clinical or pathologic entities.[2] The second most common subtype is angioimmunoblastic T-cell lymphoma. These diseases are usually nodal-based. T-cell lymphomas have a higher frequency of extranodal involvement than B-cell lymphomas, so it is also common for lesions to develop on the skin, in the bone marrow, or in other organs. Other common subtypes include systemic anaplastic large-cell lymphoma (ALCL). The remaining subtypes are much more rare.

In the United States, the incidence is between 7000 to 10,000 cases a year. The incidence varies according to how PTCL is defined. The term generally refers to the more aggressive systemic T-cell lymphomas, but other types are sometimes included within this category. Mycosis fungoides, the most common form of cutaneous T-cell lymphoma, is by strict definition a subtype of PTCL because it is a cancer of the postthymic T-cell. Cutaneous T-cell lymphomas are usually more slow-growing or indolent T-cell lymphomas that present in the skin. Many patients with more indolent cutaneous T-cell lymphoma have a long or normal life expectancy.

H&O What are the current frontline management approaches for the most common subtypes of PTCL?

SH Treatment choices are guided primarily by phase 2 studies and retrospective data. There are guidelines from the National Comprehensive Cancer Network and European organizations.[3,4] However, the current level of evidence for the treatment of T-cell lymphoma is relatively low.

The 2 most common subtypes, PTCL-NOS and angioimmunoblastic T-cell lymphoma, present as fairly aggressive systemic disease. Most of these patients respond to combination chemotherapy, such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); CHOP plus etoposide (CHOEP); or etoposide, prednisone, vincristine, cyclophos-

phamide, and doxorubicin (EPOCH). The overall response rates for those regimens are approximately 75% to 80%.[5,6] The complete response rates range from approximately 40% to 50%. Retrospective data and intent-to-treat analyses suggest that chemotherapy alone achieves a durable remission in less than 30% of patients. Most patients will either not achieve a complete response or relapse after their response.

Among patients who achieve a complete response to combination chemotherapy, approximately 40% will maintain a long-term remission.[7] Some phase 2 data and retrospective analyses support the use of autologous stem cell transplant after chemotherapy. An intent-to-treat analysis of a large phase 2 study showed a long-term remission rate of approximately 40% among patients receiving combination chemotherapy, such as CHOEP, followed by autologous stem cell transplant.[8] When the analysis was limited only to patients with a complete response, that number increased to approximately 60%.[9] For patients with PTCL-NOS or angioimmunoblastic T-cell lymphoma, treatment with aggressive combination chemotherapy offers a high chance of overall response and a good chance of complete response, but a lower chance of long-term remission. Rates of long-term remission may be increased by adding consolidation with autologous stem cell transplant, but a randomized trial would be needed for confirmation. A registry study that included comparison with unmatched controls showed that the addition of autologous stem cell transplant may increase the long-term remission rate by as much as 20%.[10] This analysis included more than 700 patients with T-cell lymphoma, some treated with an intent to transplant. Similar trends can also be seen in our institutional data. The question remains, however, whether the benefits after transplant are at least partially attributable to patient selection, which may include those who are healthier overall and have better responses to chemotherapy.

The next most common subtype is ALCL, which may be systemic or primary cutaneous. Primary cutaneous ALCL is an indolent lymphoma that usually does not require combination chemotherapy. Patients with systemic ALCL can be divided into those who express the ALK protein and those who do not. In general, patients with ALK-positive ALCL tend to be younger and to have more favorable prognostic characteristics. Most of these patients will be cured with combination chemotherapy, such as CHOP or CHOEP. This favorable prognosis erodes somewhat among patients who are older than 40 years and those who have adverse risk factors as identified by the International Prognostic Index, such as more advanced stage, poor performance status, extranodal involvement, and high levels of lactate dehydrogenase. When the chances of achieving long-term remission with chemotherapy are no greater than 50%, one option is to increase the intensity of therapy. This approach is controversial, but at our institution, we consider the use of stem cell transplant in higher-risk, ALK-positive ALCL.

In patients with ALK-negative disease, the prognosis is typically similar to that of patients with PTCL-NOS or angioimmunoblastic T-cell lymphoma, who achieve long-term remission rates of approximately 30% with combination chemotherapy. Patients with ALCL appear to do better in studies of more intensive management, such as regimens that add agents such as etoposide or include autologous stem cell transplant during first remission. In a prospective study of CHOEP plus autologous stem cell transplant, long-term remission rates were more than 60% among patients with ALK-negative ALCL who received intensive treatment.[8]

In a recent series of ALCL patients from the Mayo Clinic, those with ALK-positive ALCL did well, as expected.[11] This study also analyzed genetic markers such as mutated dual-specificity phosphatase 22 (*DUSP22*), which was found in a subset of patients with ALK-negative disease. These patients (*DUSP22* rearranged) had a very favorable prognosis, similar to that seen in ALK-positive disease. The question arises as to whether ALCL patients with ALK-negative disease who do well with aggressive therapy are enriched for DUSP22, making it unclear whether the disease or the therapy is driving the better prognosis. Patients with another mutation, in *TP63*, did poorly.

Even within the ALK-negative ALCL population, there appears to be different disease patterns. If it is confirmed that different molecular patterns are linked to prognosis, it will be necessary to determine whether mutations have impacted the results of clinical trials. It may be necessary to consider mutations when assessing the results of treatment. Our understanding of the true prognosis of patients with ALK-negative ALCL is evolving.

H&O How many patients develop relapsed or refractory PTCL?

SH The majority of patients with PTCL will eventually develop relapsed or refractory disease. Combination chemotherapy followed by upfront transplant is the most effective treatment approach in phase 2 studies, and it is associated with long-term remission rates of approximately 45% in phase 2 studies.[5,6] Therefore, even among patients who are eligible for transplant—who are younger and more robust than the overall population—the cure rate is still less than half. These aggressive therapies may be precluded in those with comorbidities and the elderly. Most of these patients will not achieve a complete response or will relapse.

H&O What are the management options for patients with relapsed or refractory disease?

SH In this setting, the approved drugs are pralatrexate (Folotyn, Spectrum), romidepsin (Istodax, Celgene), belinostat (Beleodaq, Spectrum), and brentuximab vedotin

(Adcetris, Seattle Genetics), which is approved specifically for patients with systemic ALCL. Use of these agents is supported by well-designed, reasonably sized, phase 2 trials. Comparative studies are lacking, but there are ongoing randomized trials.

Registry and single-institution data are mixed and complicated by selection biases, but they do suggest that the use of autologous or allogeneic stem cell transplant leaves a portion of relapsed/refractory patients disease-free for the long-term. Higher long-term remission rates of more than 50% are seen with allogeneic stem cell transplant, but the patients who undergo this riskier procedure must meet more selective criteria. The lower rates of long-term remission for autologous stem cell transplant in those who did not receive it as part of their initial therapy may indicate that the procedure is less reliably curative, or that it has been used in a broader range of patients. Long-term remission after autologous stem cell transplant is highest among ALCL patients who achieve a second remission.

H&O What are the clinical trial data supporting the use of new agents?

SH Data for the newer agents are sometimes better understood than the data supporting the use of older agents, which are often extrapolated from other diseases. Pralatrexate, belinostat, and romidepsin were approved based on phase 2 trials showing overall response rates of 29%, 26%, and 25%, respectively.[12-14] Among patients who respond, remissions can often be maintained for 6 to 12 months with continuous therapy. However, the median progression-free survival is 3 to 4 months, which is similar to that seen with older agents.

Brentuximab vedotin is approved for ALCL based on results from a phase 2 study showing an overall response rate of 86%.[15] More than half of patients had complete responses, many of which lasted a year or longer. Brentuximab vedotin targets CD30, and in studies of other T-cell lymphomas that express this antigen, response rates are more similar to those seen with the other approved agents. In patients with T-cell lymphoma, studies are evaluating brentuximab vedotin added to a CHP regimen (CHOP that excludes the vincristine) based on concerns about overlapping neuropathy. In a phase 1 trial, the combination of brentuximab vedotin was safe and appeared promising.[16] An ongoing randomized phase 3 study is evaluating brentuximab vedotin plus CHP vs CHOP among T-cell lymphoma patients with expression of CD30.[17]

H&O What other regimens are being studied in ongoing trials?

SH Romidepsin was being combined with CHOP in a phase 1b/2 study[18] and is also undergoing evaluation in a large European phase 3 study randomizing patients to receive romidepsin plus CHOP or CHOP alone.[19] The goal is to determine whether romidepsin can improve the response rate, progression-free survival, and, hopefully, overall survival of patients with T-cell lymphoma.

Belinostat and pralatrexate are now being studied in combination with CHOP. A study in which pralatrexate was administered after CHOP as maintenance therapy was closed early owing to lack of accrual. In a small study, the response rate of pralatrexate alternating with cyclophosphamide, etoposide, vincristine, and prednisone was similar to that seen with CHOP alone.[20] Two phase 1 studies are evaluating pralatrexate plus CHOP and belinostat plus CHOP.[21] The tentative plan, based on accelerated approval from the US Food and Drug Administration, is to conduct larger randomized studies comparing belinostat plus CHOP vs CHOP alone and pralatrexate plus CHOP vs CHOP alone.

The novel agent alisertib, an inhibitor of Aurora kinase A, appeared promising in phase 2 studies.[22,23] A randomized trial in the relapsed setting comparing alisertib to single agents such as pralatrexate, romidepsin, and gemcitabine was stopped early after an interim analysis failed to show any likely benefit for alisertib over the available standard therapies.

H&O How do newer agents improve upon existing treatment regimens?

SH Many of the newer agents simply present an additional option. The majority of patients will not have a meaningful response to these agents, but a significant minority will respond and show some durable disease control. The greater hope is that these agents can improve survival by extending disease control. No data show that any agent improves median overall survival, but there are individual patients with poor prognoses who have had good disease control for months or even several years and beyond. Unfortunately, it is not yet possible to predict which patients will respond well to these agents. The hope for these new agents is to incorporate them into frontline therapy and cure more people upfront. Studies evaluating this approach are ongoing.

There are several agents in development. The PI3 kinase inhibitor duvelisib, the IDH2 inhibitor AG-221, and other novel drugs and combinations are being studied in relapsed disease.

In addition to seeing if any of the newer agents improve results when combined with standard chemotherapy, we also hope to find predictive biomarkers to help select therapy for individual patients. A long-term goal is to develop combination therapies that are rationally designed for patients with certain subsets or profiles of T-cell lymphoma, leading to better survival for all.

H&O Do you have any suggestions on how to incorporate newer agents into the treatment course?

SH The best way for patients to access new agents is in clinical trials. There is theoretically (and hopefully) a benefit to incorporating newer agents in earlier lines of therapy, but clinical trials are needed for assessment of safety and to understand and confirm any benefit. Currently, there are no compelling data that indicate how to sequence or select therapy for individual patients in the upfront setting, but studies are underway. In the relapsed setting, some of the newer agents have specific targets. For example, clinical data indicate that brentuximab vedotin would be preferable earlier in the treatment of relapsed ALCL as compared with other novel agents.[15] (Outside of the ALCL setting, it is unclear whether the degree of CD30 expression, if any, can be used to predict response.)

H&O What are some areas of research in PTCL?

SH A main area of research is the evaluation of new agents, including how they work and in which patients. In the relapsed setting, more active agents that can achieve a response and maintain remission are needed. There is also a need for better upfront therapies that cure more patients. The best chance of cure and a positive long-term outcome is with first-line therapy. It is clear that new drugs will be needed in this setting.

Several studies in the past few years have used mutational profiling to identify recurrent mutations in subsets of T-cell lymphoma. Mutations in AITL include IDH2, TET2, and more commonly, RHOA. Studies are underway to identify agents that would be better targeted toward specific types of T-cell lymphoma and to elucidate predictors of response or mechanisms of resistance. The likelihood is low that a single agent will provide a long-term solution for most patients. Studies are trying to combine agents in a more rational way to build better combination regimens.

Chemotherapy works for many patients, but its use is primarily empiric. There are deficiencies with the standard combination chemotherapies for T-cell lymphoma. The ability to identify more mechanistically based combination therapies may lead to more tailored therapy and, hopefully, better overall results.

Disclosure

Dr Horwitz has received consulting fees from Celgene, Millennium, Kyowa Hakko Kirin, Seattle Genetics, and Spectrum. He has performed contracted research for Celgene, Millennium, Seattle Genetics, Infinity, Kyowa Hakko Kirin, and Spectrum.

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