Emerging Approaches for Patients With Less Common Lymphomas

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Overview
This activity is designed to inform physicians about the latest treatment advances and data in less common lymphomas, focusing on the field of Hodgkin lymphoma and T-cell lymphoma, including both recently approved and investigational treatment strategies.

Target Audience
This activity is directed toward hematologists, medical oncologists, nurses, and nurse practitioners who manage and treat patients with lymphoma. Transplantation specialists, radiation oncologists, pathologists, fellows, physician assistants, and other healthcare providers interested in the treatment of lymphoma are also invited to participate.

Learning Objectives
After participating in this CME activity, learners should be better prepared to:
- Summarize data with anti-CD30 immunoconjugates following stem-cell transplant in patients with high-risk Hodgkin lymphoma
- Discuss efforts to reduce the toxicity of ABVD therapy in patients with Hodgkin lymphoma
- Review the use of agents, which have been used to target B-cell signaling, that also have potential targets in T-cell lymphoma
- Identify potentially favorable subsets of patients with ALK-negative anaplastic large cell lymphoma

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Hodgkin Lymphoma

The therapy of Hodgkin lymphoma represents one of the major advances of oncology, and for the 9,050 patients expected to be diagnosed in the US in 2015, approximately 80% can expect a cure, even those with advanced disease.[1,2] In advanced disease, combination chemotherapy is a common first-line approach, including doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) or escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone (eBEACOPP).[2] For patients with relapsed disease, approaches include other chemotherapy regimens such as ifosfamide, carboplatin and etoposide (ICE), epirubicin in place of carboplatin (IVE), and cytarabine and cisplatin (DHAP).[2] Patients achieving a complete response to second-line therapy typically are considered for autologous stem cell transplant (ASCT).[2]

Despite the curative advances in Hodgkin lymphoma, not all patients are cured, and significant short- and long-term toxicities may occur with combination chemotherapy or combined modality approaches. Therefore, despite the overall favorable prognosis, new therapeutic approaches are still needed. One of these agents, the antibody-drug conjugate brentuximab vedotin, targets the CD30 molecule, which is expressed on Hodgkin lymphoma cells.[3] Based on the results of a phase 2 trial, brentuximab vedotin was approved in August 2011 by the US Food and Drug Administration (FDA) for patients with relapsed disease.[4] In August 2015, brentuximab also received US FDA approval in patients with high-risk Hodgkin lymphoma as consolidation following ASCT based on the phase 3 AETHERA trial.[5] In this study, 329 patients with relapsed or primary refractory Hodgkin lymphoma received brentuximab vedotin or placebo following ASCT. The primary endpoint of progression-free survival was significantly improved in the brentuximab vedotin arm (42.9 months vs. 24.1 months; $P = .0013$); an interim analysis showed no difference in overall survival. Increases in sensory neuropathy (56% vs. 16%) and neutropenia (35% vs. 12%) were also reported in the brentuximab vedotin arm; 85% of the patients in the brentuximab vedotin arm had resolution or improvement of neuropathy, with a median time to resolution of 23.4 weeks. Additional studies with brentuximab vedotin in patients with Hodgkin lymphoma are in progress, including in the frontline setting.

Immune checkpoint inhibitors have also recently shown preliminary evidence of activity in patients with Hodgkin lymphoma. The anti-PD-1 antibody nivolumab demonstrated an overall response rate (ORR) of 87% in 23 patients with heavily pretreated disease, including a complete response rate of 17%.[6] Grade 3 adverse events included 1 case each of lymphopenia, elevated lipase, and stomatitis. Data from pembrolizumab, which also targets PD-1, have been reported from 29 patients who previously experienced treatment failure with brentuximab vedotin.[7] The ORR was 66%, including a complete response in 21% of the patients. Grade 3 pneumonitis and colitis were each reported in 1 patient. Additional studies with immune checkpoint inhibitors, including registration trials, are currently ongoing in Hodgkin lymphoma.

Peripheral T-Cell Lymphoma

Approximately 6000 cases of peripheral T-cell lymphoma are diagnosed every year in the US.[8] Due to the lack of an optimized therapeutic strategy for these patients, enrollment on a clinical trial remains the approach of choice.[8] For patients who must seek treatment off protocol, multi-agent chemotherapy based on regimens for B-cell lymphomas are most commonly used. In patients younger than 60 years of age, cyclophosphamide, doxorubicin, vincristine, prednisone, and etoposide (CHOEP) is recommended by some, while CHOP alone appears better tolerated for elderly patients; eligible patients are referred to consolidation with ASCT.[8] One important exception is in patients with anaplastic large cell lymphoma that expresses the anaplastic lymphoma kinase (ALK); patients in this subset have a relatively good prognosis with combination chemotherapy alone.[9]

A wide range of agents have been approved for patients with relapsed/refractory disease, including the antifolate pralatrexate, the histone deacetylase (HDAC) inhibitors romidepsin and belinostat, and the antibody-drug conjugate brentuximab vedotin.[8] In an effort to improve frontline therapy, phase 3 trials are currently under way to examine the addition of romidepsin or brentuximab vedotin to chemotherapy in previously untreated patients with T-cell lymphomas.

For patients with ALK-positive anaplastic large cell lymphoma, chemotherapy is still the first-line standard of care. However, the ALK inhibitor crizotinib, which is approved in lung cancer, has shown initial evidence of activity in a subset of patients with lymphoma. In a series of 11 patients with chemotherapy-resistant, ALK-positive lymphomas (9 anaplastic large cell lymphoma, 2 diffuse large B-cell lymphoma), the overall response rate was 91%.[10] All 9 patients with anaplastic large cell lymphoma achieved a complete response.

Other targeted agents have demonstrated activity in patients with T-cell lymphoma. For example, duvelisib, an inhibitor of the delta and gamma isoforms of phosphatidylinositol 3-kinase, yielded responses in 42% of 31 evaluable patients with relapsed/refractory T-cell lymphoma, including 2 complete responses.[11] The most common grade ≥3 adverse events included elevated liver enzymes (36%) and rash (21%).

Moderator: Brentuximab vedotin following autologous stem-cell transplant (ASCT) was recently approved in patients with Hodgkin lymphoma who have a high risk of relapse, based on improved PFS. Given the similar OS between the 2 arms, what is your approach regarding the use of brentuximab vedotin in this setting?

Dr. Horwitz: The AETHERA trial enrolled patients with relapsed or refractory Hodgkin lymphoma who had certain high-risk features that made them more likely than others to relapse after transplant,

and then randomized them to brentuximab vedotin or placebo. And there was an improvement in PFS, which was statistically significant, and it's probably clinically meaningful.

So I'm incorporating the AETHERA data pretty much as per study with a few tweaks. The study defined high risk factors as extranodal disease or short remission of less than a year, primary refractory disease, or the presence of B symptoms. I think our data also suggest that those who go into transplant with residual PET-avid disease also are at higher risk of relapse. In a patient who's eligible to get that therapy post transplant, I would discuss it with them, but would usually give it. If there was someone who didn't want it or who had significant baseline neuropathy, or if I was more worried about comorbidities, one could follow them expectantly and just treat with brentuximab vedotin if progression occurs.

In this study, overall survival was similar, with subjects doing well in both arms. There's no sense that the overall survival was similar because patients on brentuximab vedotin who had better PFS were having more life threatening toxicity. So even though overall survival is similar, as patients are coming off high dose therapy, I lean towards giving it, and believe that remaining in remission provides real clinical benefit for most patients.

Moderator: We have seen some encouraging initial results with immune checkpoint inhibitors in patients with Hodgkin lymphoma. What are the next steps being taken? If approved, how would these agents fit into the treatment paradigm relative to the other therapeutic options available?

Dr. Horwitz: The data look really promising. There are high response rates that have been seen with both nivolumab and pembrolizumab, and there's certainly a potential role if those drugs get approved. But most patients with Hodgkin lymphoma are cured with upfront therapy. If they're not cured with upfront therapy, they're often cured with ASCT in relapse and now, as we just talked about in the AETHERA study, you're improving results even for high-risk patients after ASCT. It's always challenging to take a group of patients who are likely to be cured with standard therapy, even chemotherapy, and give them a new drug that has a lot of promise but also some toxicity. But certainly those patients who progress following ASCT is one setting where new therapies are needed. Another potential population is patients in the relapsed setting who, for whatever reason, are not proceeding to ASCT or choose not to undergo ASCT, and some of the responses there have been durable.

There are ongoing and planned studies combining immune checkpoint inhibitors with brentuximab vedotin. There is also a subset of patients with Hodgkin lymphoma that we can identify as having a higher risk of not being cured, and there's interest in incorporating immune checkpoint inhibitors into earlier lines of therapy for patients with higher-risk disease.

Moderator: Activity with agents that are generally classified as BCR pathway inhibitors (eg, PI3K inhibitors) has also been observed in patients with T-cell lymphomas. Can you comment on the potential of these agents in T-cell lymphoma and if this is being investigated further?

Dr. Horwitz: I think we have had the most experience with duvelisib, which is a dual PI 3-kinase gamma/delta inhibitor. We participated in a study enrolling patients with a broad range of hematologic malignancies. This was a phase 1 trial with expansion cohorts, including about 33 evaluable patients with T-cell lymphomas, both peripheral T-cell lymphomas and cutaneous T-cell lymphomas. And, particularly among the peripheral T-cell lymphoma cohort, which was only 15 patients, we saw a response rate exceeding 50%, which is quite good compared to some of the other agents we have in T-cell lymphoma. Some of the responses were relatively durable, although this was, of course, a non-comparative study. We have one patient who had relapsed PTCL who has now been in continuous remission for more than 2 years on that drug.

So we think there's promising activity. One of the questions we have is: is that activity across the board and should we look at this as a single agent? We already have several approved single agents in relapsed T-cell lymphoma and in general I think combinations have the potential to provide greater benefit to our patients. As this drug has a mechanism that could be understood better, we would like to develop predictive biomarkers to select where this drug is more likely to work and design optimal combinations. So right now we're very interested in targeting the PI 3-kinase pathway and looking at how inhibitors might behave as part of combination therapy, and we have some early phase combination studies in development.

In terms of other agents, we do have a study looking at ibrutinib. It's well known that ibrutinib targets Bruton's tyrosine kinase (BTK), which is not expressed in T-cell lymphoma, except aberrantly in very rare cases. However, ibrutinib can inhibit the interleukin-2-inducible T-cell kinase (ITK), and ITK is overexpressed and may be important in some T-cell lymphomas. So right now, we're interested in an early look at ITK inhibition, to see if it's feasible at reasonable doses of ibrutinib, and whether or not ITK inhibition is of benefit for patients with T-cell lymphoma.

Moderator: Can you comment on other emerging molecular targets for patients with T-cell lymphomas?

Dr. Horwitz: When we and others have looked at mutational profiling of T-cell lymphomas, we saw a number of recurrent mutations in genes such as *TET2*, which suggests aberrancy in methylation. Hypomethylating agents might be a reasonable strategy in this situation, but have really not been very well investigated in T-cell lymphomas. In particular, in angioimmunoblastic T-cell lymphoma, we've seen a fair number of cases with *TET2* and *DNMT3A* mutations. So far, this has not been extensively explored therapeutically, but that's something of interest. Additionally, in angioimmunoblastic T-cell lymphoma, about 20%-30% of cases carry an *IDH2* mutation. There are oral IDH inhibitors that have shown preliminary activity in acute leukemia, and those are drugs that we and others are looking at in the subset of patients with angioimmunoblastic T-cell lymphoma and *IDH2* mutations.

I think once you get past that in T-cell lymphomas, there are aberrations in JAK/STAT signaling, there are aberrations in SYK, and there's a number of other potential molecular targets, but they are often in small subsets of patients.

The best example we have of a proof of principle of kinase inhibition or other molecular targets as a therapeutic strategy in T-cell lymphoma is crizotinib, the ALK inhibitor that is approved in lung cancer. There is a subset of patients with anaplastic large-cell lymphoma (ALCL) whose disease expresses the ALK protein. And there are small series of patients with relapsed, ALK-positive ALCL treated with crizotinib, including one where all 9 subjects with ALK-positive ALCL responded completely. And as we're learning more about some of the recurrent mutations in T-cell lymphoma, the hope is that we'll be able to identify some better targeted therapies to add to or improve upon our current tools.

Moderator: In DLBCL, the use of molecular markers for subtyping has revealed potential approaches for high-risk subgroups (eg, ABC-DLBCL). For patients with less common lymphomas, such as T-cell lymphoma or Hodgkin lymphoma, what is the status of identifying subgroups for better tailoring therapy?

Dr. Horwitz: In Hodgkin lymphoma, a gene expression signature or extent of macrophage infiltration has been associated with a poorer prognosis. In T-cell lymphoma, there is a T-follicular helper cell phenotype that is a feature of angioimmunoblastic T-cell lymphoma, and some patients with unspecified peripheral T-cell lymphoma have more of that signature. Those patients are going to be grouped together in upcoming classification systems. We don't know yet that it will lead to differential approaches to therapy, however. There's some very early evidence that the HDAC inhibitors may be more effective in patients with angioimmunoblastic T-cell lymphoma, and those cases do seem to have more clustering of mutations in epigenetic modifiers.

There are also data from one series that T-cell lymphoma patients who have more of a cytotoxic phenotype or what's been called GATA-3 high tumors appear to have a worse prognosis. Again, this is not truly being used to select therapy, but may help identify who is less likely to be cured with standard therapy, which might favor enrollment of these patients on clinical trials.

I think the only thing that is closer to being ready for prime time is in patients with systemic anaplastic large-cell lymphoma. Among systemic ALCL, there are those who are ALK-positive who have a relatively better prognosis, and those that are ALK-negative and who have a relatively worse prognosis. There is a recent paper from the Mayo Clinic where among the ALK-negative patients, they identified a subset with a *DUSP22* rearrangement, and they had a very favorable outcome similar to those with ALK-positive anaplastic large-cell lymphoma.

We often think about taking patients with poor-prognosis T-cell lymphoma to a front-line transplant, and the question that these data raise is, if you really have this *DUSP22* rearrangement, might you do just as well without consolidation? Some people have adopted this approach. It would be nice to have a confirmatory series before changing practice, because we currently have data from only 1 series. But the data are fairly compelling that the *DUSP22* rearrangement correlates with a more favorable prognosis, and that good prognosis may be achieved without consolidation.

Moderator: Finally, which upcoming trials have the potential to change the standard of care for patients with T-cell lymphoma or Hodgkin lymphoma?

Dr. Horwitz: I think for Hodgkin lymphoma, we've recently seen some important data. The RAPID trial looked at short course chemotherapy for early stage disease, and randomized PET-negative patients to receive either radiation therapy or no further treatment. The 3-year progression free survival was very good for both arms, 95% with radiation therapy and 91% without. The study technically did not meet the noninferiority endpoint, but provides data to support excellent outcomes with either approach, which physicians can use to individualize therapy for their patients. There is also the RATHL trial, which was presented at the Lugano meeting this past summer, which looked at dropping bleomycin from ABVD in cycles 3-6 of therapy in patients with early PET-negative scans and escalating therapy in those who did not convert to early PET negativity.

There are randomized studies incorporating brentuximab vedotin into upfront therapy for advanced-stage Hodgkin lymphoma, omitting the bleomycin due to toxicity. And there's some smaller studies looking at the incorporation of brentuximab vedotin into initial therapy for elderly Hodgkin patients.

I think that's all data we're going to have within the next few years that may be practice changing. In terms of the immune checkpoint inhibitors in Hodgkin lymphoma, in the short term, those are going to be in the relapsed/refractory setting as single-agents. The studies that will investigate these agents in combination or in earlier lines of therapy may be a little further off.

With T-cell lymphoma, we have two randomized studies in the upfront setting which are ongoing and hopefully will be finished soon. One of those is investigating brentuximab vedotin with CHP versus CHOP for patients with untreated T-cell lymphoma who have at least a minimal amount of CD30 expression. Results from that study are probably still a couple of years away. And then there's a randomized study looking at romidepsin in combination with CHOP versus CHOP alone to see if the addition of romidepsin can change the outcome in the upfront setting in patients with peripheral T-cell lymphoma.

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