

# ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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## Consolidation Therapy After Autologous Stem Cell Transplant in Relapsed/Refractory Hodgkin Lymphoma



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**H&O** Approximately how many patients with Hodgkin lymphoma progress after autologous stem cell transplant?

**CM** The number of patients with Hodgkin lymphoma undergoing transplant is decreasing because of better upfront therapy. In the United States, approximately 55% to 60% of patients with relapsed/refractory Hodgkin lymphoma are cured with salvage therapy followed by a stem cell transplant. Approximately 40% of patients need additional therapy.

**H&O** How is relapse after autologous stem cell transplant defined?

**CM** Relapse is defined by biopsy-proven disease. In general, patients undergo imaging every 6 months for the first 2 years. Afterward, the imaging schedule varies across centers. I usually image again at 3 years. I usually stop at this point because the risk of relapse after 3 years is so low. The data show that relapse after stem cell transplant tends to occur between 3 and 12 months posttreatment. In general, approximately half of the patients who relapse will do so within the first 6 to 9 months posttreatment. Among the remaining patients, half will relapse between 9 and 15 months posttreatment, and the other half will relapse between

15 and 24 months afterward. Probably less than 5% of patients will relapse after a stem cell transplant once they have been in remission for 24 months.

**H&O** What is the mechanism of action of brentuximab vedotin?

**CM** Brentuximab vedotin (Adcetris, Seattle Genetics) is an antibody-drug conjugate. It consists of an antibody to CD30, located on the Reed-Sternberg cells, which is linked to the chemotherapy prodrug monomethyl auristatin E (MMAE). Hodgkin lymphoma is defined by being CD30-positive. Brentuximab vedotin is the first of many antibody-drug conjugates. It binds to CD30, the antibody is then internalized, and MMAE is released within the cell. MMAE is enzymatically cleaved and binds to the tubulin inhibitor, which causes direct cell kill.

**H&O** What prompted the phase 3 AETHERA study, which evaluated brentuximab vedotin in relapsed/refractory Hodgkin lymphoma?

**CM** The AETHERA study (A Phase 3 Study of Brentuximab Vedotin [SGN-35] in Patients at High Risk of Residual Hodgkin Lymphoma Following Stem Cell Transplant) was prompted by the fact that it is possible to predict fairly reliably which patients will do

extremely well with a stem cell transplant. These patients have nodal-only relapse, have not received treatment with radiation therapy, and relapsed after a year. In general, however, most patients with nodal-only disease who achieve a remission from their salvage therapy do well, regardless of when they relapse. We knew in 2009, when the trial design began, that poorer outcomes were seen in patients who had disease outside of the lymph node system, patients who had primary refractory disease, and patients who did not achieve a remission with salvage chemotherapy. When we designed the AETHERA study, we required patients to have at least 1 risk factor for enrollment. The reason is that their cure rate is less than 50%, when all of the pretransplant risk factors are counted. We believed that those patients would benefit from a drug with activity given posttransplant in the maintenance setting.

### H&O Could you please discuss the trial design?

**CM** The AETHERA study was the largest study done in relapsed or refractory Hodgkin lymphoma. It was a placebo-controlled, random-assignment trial enrolling patients who had remission duration of less than a year, primary refractory disease, or extranodal involvement prior to salvage chemotherapy. Prospective patients received salvage chemotherapy, which was usually platinum-based, at their own institution. Provided that the disease was responding, they underwent a stem cell transplant. Within 45 days after stem cell transplant, patients were eligible for enrollment in the AETHERA study. The study compared brentuximab vedotin vs placebo for up to 16 doses, with 1 dose given every 3 weeks. The primary endpoint was 2-year progression-free survival.

### H&O What were the findings?

**CM** At 3 1/2 years of follow-up, 61% of the patients who received brentuximab vedotin maintenance or consolidation were progression-free, vs 44% of the patients who received placebo. These patients are cured. The difference in 3-year progression-free survival shows an improvement of 17% for the patients treated with maintenance brentuximab vedotin. Will this difference translate to an overall survival advantage? It is unclear with the recent introduction of novel agents, specifically the checkpoint inhibitors. But be that as it may, a cure rate of 61% is the best result ever reported in this unfavorable cohort.

We presented updated data at the 2016 meeting of the American Society for Blood and Marrow Transplantation with an additional year of follow-up. The critical aspect in the updates is that almost no events are happening after 2 years. The curves are very robust. This October,

we will update the data once again at the International Symposium on Hodgkin Lymphoma in Cologne.

### H&O How have the results of AETHERA impacted clinical practice?

**CM** Use of brentuximab vedotin after transplant in patients with relapsed/refractory Hodgkin lymphoma is now a standard treatment. This approach was approved by the US Food and Drug Administration (FDA) and is a level 1 recommendation in guidelines from the National Comprehensive Cancer Network.

In my own treatment of patients who are in remission prior to transplant, I reserve posttransplant therapy for those who have at least 2 risk factors. The AETHERA study defined 5 risk factors: remission duration of less than 1 year, extranodal involvement, more than 1 salvage regimen received, lack of a complete response to salvage treatment, and B symptoms. Among patients who had a complete response prior to salvage therapy, I require extranodal involvement to consider posttransplant therapy. In this setting, there is no other reason for me to subject a patient to a year of treatment. Although brentuximab vedotin is an antibody-drug conjugate, it does cause significant neurotoxicity. It is not a benign drug.

An important issue concerns the use of brentuximab vedotin more proximal in the treatment course, as a component of primary management and with salvage therapy. It is not known whether patients will benefit from brentuximab vedotin after transplant if they received it already. This question was not addressed in the AETHERA study. In addition, the AETHERA study provided little data on outcome based on pretransplant positron emission tomography (PET). Two-thirds of the patients in the study had a PET scan, but these scans were not centrally reviewed.

### H&O Is it possible to identify groups of patients who benefit more from the use of brentuximab vedotin as consolidation therapy?

**CM** Any patient who is not in remission should receive brentuximab vedotin posttransplant. In addition, I firmly believe that patients with stage 4 disease before salvage chemotherapy should receive posttransplant brentuximab vedotin after salvage treatment, regardless of whether they are in remission.

### H&O Is it known whether consolidation therapy with brentuximab vedotin might be beneficial among patients with low-risk disease?

**CM** I do not think there is any role for that.

## H&O Do you anticipate any changes in the management of relapsed/refractory Hodgkin lymphoma?

**CM** In general, I believe that brentuximab vedotin should be used as part of salvage therapy pretransplant. This strategy improves the complete response rate prior to transplant, which is the single most important predictor of outcome. My colleagues and I have published data supporting this approach, and forthcoming data from other groups are expected.

The use of checkpoint inhibitors for palliation will probably become the standard of care fairly soon. It is likely that the addition of brentuximab vedotin to standard upfront chemotherapy with doxorubicin/vinblastine/dacarbazine (AVD) may become standard treatment, based on results from the ECHELON-1 study (Phase 3 Frontline Therapy Trial in Patients With Advanced Classical Hodgkin Lymphoma). We will learn in the next year or so whether this approach is established as standard treatment. If it is, then the whole treatment pathway is going to change. More patients will be cured upfront. The patients who relapse will relapse more unfavorably. It is very unlikely that patients with advanced disease who receive 12 doses of brentuximab vedotin as upfront therapy will receive retreatment with it. Much of the treatment paradigm will be based on whether patients receive brentuximab vedotin and AVD as part of primary therapy. If that happens, then the use of brentuximab vedotin in the relapsed setting will be minimal and substituted by newer agents such as nivolumab (Opdivo, Bristol-Myers Squibb) or pembrolizumab (Keytruda, Merck).

A recent key development is the FDA approval of nivolumab for patients with relapsed/refractory Hodgkin lymphoma who have already experienced a treatment failure with brentuximab vedotin. It is likely that pembrolizumab will also be approved by the end of the year in the same setting.

There are a number of brentuximab vedotin salvage programs, such as a study evaluating it with nivolumab.

There are many combination programs that we will learn about in the next year. Brentuximab vedotin is being combined with bendamustine; with etoposide, methylprednisolone, cytarabine, and cisplatin (ESHAP); and with ifosfamide, carboplatin, and etoposide (ICE). The current treatment strategy will probably change.

### Disclosure

*Dr Moskowitz has received research support from Seattle Genetics, Merck, and Pharmacyclics. He is a member of the Scientific Advisory Boards of Seattle Genetics, Merck, and Celgene.*

### Suggested Readings

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