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Is There a New Standard-of-Care Therapy for Advanced Hodgkin Lymphoma?

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H&O What has been the traditional treatment for patients with advanced Hodgkin lymphoma?

AH The traditional treatment for patients with stage III or IV Hodgkin lymphoma was combination chemotherapy with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). Treatment was administered in 6 cycles over 6 months.

Researchers designed the phase 3 ECHELON-1 trial to see if they could improve outcomes by replacing bleomycin, a drug that causes lung toxicity, with the CD30-targeting antibody-drug conjugate brentuximab vedotin (BV; Adcetris, Seagen). By 2017, BV-AVD had been found to prolong progression-free survival (PFS) and reduce lung toxicity in comparison with ABVD, leading to US Food and Drug Administration (FDA) approval and a newer standard of care in advanced Hodgkin lymphoma of 6 months of BV-AVD.[1] By 2022, BV-AVD had been shown to improve overall survival, further supporting its use.[2] The 6-year estimated overall survival rate was 94% in the BV-AVD group and 89% in the ABVD group. The downside was that BV-AVD caused more overall toxicity than ABVD did, with more infections, febrile neutropenia, and peripheral neuropathy.

H&O Could you talk about the introduction of programmed death 1 (PD-1) inhibition to treatment?

AH PD-1 blockade is a uniquely targeted therapy for Hodgkin lymphoma. Hodgkin lymphoma tumor cells have genetic alterations in the PD-1 ligands that lead to overexpression. Drugs that block PD-1, like nivolumab (Opdivo, Bristol Myers Squibb) and pembrolizumab (Keytruda, Merck), are highly effective as single agents, inducing durable remissions in most patients. However, their curative potential is lower in patients with disease already resistant to multiple treatments. We learned from the phase 3 KEYNOTE-204 trial, which compared pembrolizumab vs BV in patients who had experienced a relapse after autologous hematopoietic stem cell transplant (auto-HSCT) or were ineligible for auto-HSCT,[3] that PFS was longer with single-agent PD-1 blockade than with single-agent BV. Over time, we have moved PD-1 blockade to earlier during treatment. We have shifted from chemotherapy and radiation as the only treatments to the use of novel agents to achieve remission when initial chemotherapy fails. We also have been able to move PD-1 inhibitors to earlier lines of therapy. Instead of using them for patients with highly resistant disease, now we can use

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them before auto-HSCT. This allows approximately 90% of patients to achieve remission before proceeding to potentially curative treatment with auto-HSCT.

The multicenter, open-label, randomized phase 3 S1826 trial involved multiple cooperative groups: the Southwest Oncology Group, the Alliance, the Eastern Cooperative Oncology Group, the Canadian Clinical Trials Group, and the Children's Oncology Group. Although historically pediatric patients with Hodgkin lymphoma were treated differently than adults, we harmonized the treatment approach for both adolescents and adults in this study. S1826 enrolled patients at least 12 years of age who had newly diagnosed stage III or IV Hodgkin lymphoma. Patients were randomly assigned in a 1:1 ratio to nivolumab plus AVD or to BV-AVD as frontline therapy. Patients could receive consolidative radiation therapy to lesions that were residually fluorodeoxyglucose-avid on positron emission tomography. Patients in the BV arm were required to receive granulocyte colony–stimulating factor (G-CSF) to prevent a reduction in the white blood cell count; the use of G-CSF in the nivolumab arm was optional. The primary endpoint was PFS.

> Studies are ongoing to incorporate brentuximab vedotin and PD-1 inhibitors into treatment for early-stage Hodgkin lymphoma.

We enrolled 996 patients with advanced-stage Hodgkin lymphoma in the S1826 study. Approximately 25% of the patients were younger than 18 years, and 10% were older than 60 years. This is important because outcomes in older patients with Hodgkin lymphoma who receive treatments like ABVD and BV-AVD are typically worse than outcomes in younger patients; improving outcomes for older patients is a crucial unmet need. The poorer outcomes are due to differences in the disease biology and the fact that older adults are less able to tolerate treatment—especially BV-AVD, which is a particularly challenging regimen for older patients. Another important characteristic of the patient population is that it was diverse; one-quarter of the patients were Hispanic or Black. Overall, we enrolled a very representative group of patients with advanced-stage Hodgkin lymphoma.

In the S1826 study, we found that nivolumab-AVD was better tolerated than BV-AVD, with less neuropathy, less need for growth factors, and fewer gastrointestinal toxicities. Although more neutropenia occurred with nivolumab-AVD because growth factor injections were not required, infections did not increase. Although immune-related toxicities are well-known to occur with PD-1 inhibitors, immune-related adverse events were infrequent with nivolumab, and the immune toxicity rates in this study were similar in the 2 arms. More patients in the BV arm discontinued treatment early, and BV dose reduction was common.

Our study enrolled patients during the COVID pandemic, and with the tremendous enthusiasm for the study in the cooperative groups, we completed enrollment a year ahead of time. At a median follow-up of 12.1 months, PFS was significantly longer with nivolumab-AVD than with BV-AVD (hazard ratio for disease progression or death, 0.48; 99% CI, 0.27-0.87; 2-sided P=.001). The 1-year PFS rate was 94% with nivolumab-AVD vs 86% with BV-AVD. Because the aim of therapy for advanced lymphoma is to cure the disease, we waited for 2-year data, which we have now published in *The New England Journal of Medicine*.[4] At a median follow-up of 2.1 years, the 2-year PFS rate was 92% with nivolumab-AVD and 83% with BV-AVD, confirming a substantial improvement in durable remission. The benefit of nivolumab-AVD was consistent across patient subgroups based on factors such as age, cancer stage, and International Prognostic Score.

Most pediatric patients typically receive consolidative radiation, but fewer than 1% of patients received radiation in the S1826 study. We showed that with the incorporation of nivolumab into treatment, radiation was unnecessary for nearly all patients, potentially reducing the late toxic effects of radiation therapy. On the basis of these results, nivolumab-AVD is now a new standard of care for stages III and IV Hodgkin lymphoma. We are working on an FDA submission and guideline updates.

H&O Are there other groups of patients with Hodgkin lymphoma who might benefit from novel regimens?

AH Studies are ongoing to incorporate BV and PD-1 inhibitors into treatment for early-stage Hodgkin lymphoma. The phase 3 AHOD2131 study from the Children's Oncology Group is comparing the use of BV plus nivolumab vs standard chemotherapy with or without radiation in patients (aged 5-60 years) with newly diagnosed, previously untreated stage I or II Hodgkin lymphoma (NCT05675410). The next steps may involve using biomarkers, blood tests, or imaging markers to tailor therapy by reducing chemotherapy if the patient

responds well. This may especially benefit young patients, who experience the most harm from long-term treatment side effects.

H&O What considerations exist for pregnant patients?

AH ABVD has been well studied during pregnancy, and the combination is safe to use after the first trimester in patients with Hodgkin lymphoma. We have not studied BV or PD-1 inhibitors during pregnancy, so they are not recommended for these patients.

Disclosures

Dr Herrera has served in a consulting or advisory role to Bristol Myers Squibb, Seagen, Merck, Genentech/Roche, AstraZeneca/MedImmune, Karyopharm Therapeutics, ADC Therapeutics, Takeda, Regeneron, Genmab, Tubulis GmbH, Pfizer, Adicet Bio, Caribou Biosciences, AbbVie, and Alimera Sciences; and has received research funding to institution from Bristol Myers Squibb, Merck, Genentech/Roche, Kite/Gilead, AstraZeneca, Seagen, Gilead Sciences, and ADC Therapeutics.

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