

# Integrating Novel Agents in Relapsed or Refractory Hodgkin Lymphoma: Highlights From SOHO 2020

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At the 2020 SOHO Annual Meeting, Alex F. Herrera, MD, of City of Hope, discussed the integration of novel agents into the management of patients with relapsed or refractory Hodgkin lymphoma. **Kelly Valla, PharmD, BCOP**, of Winship Cancer Institute of Emory University, discusses insights from this session for advanced practitioners.

**C**andidate therapies for relapsed Hodgkin lymphoma need to exceed a high bar of response set by existing salvage approaches, all while being less toxic than available options. Various combination chemotherapy regimens yield high response rates but are fraught with hematologic adverse effects (Baetz et al., 2003; Bartlett et al., 2007; Josting et al., 2002; Moskowitz et al., 2015; Santoro et al., 2007; Santoro et al., 2016).

## BRENTUXIMAB VEDOTIN AND PD-1 BLOCKADE

The approvals of brentuximab vedotin (Adcetris), nivolumab (Opdivo), and pembrolizumab (Keytruda) are hallmarks in the advancement of the management of relapsed Hodgkin lymphoma (Seagen Inc, 2020; Bristol-Myers Squibb Company, 2020; Merck Sharp & Dohme Corp, 2020). In fact, benefits seen with brentuximab vedotin in

relapsed/refractory patients as well as when used with a consolidative intent after autologous stem cell transplant sparked interest that led to the landmark ECHELON-1 study, ultimately earning this agent a space in frontline therapy when combined with doxorubicin, vinblastine, and dacarbazine, or A-AVD (Connors et al., 2018).

Emerging data also exist for incorporating anti-programmed cell death protein 1 (PD-1) therapy in the frontline setting. In fact, in the ongoing Southwest Oncology Group (SWOG) S1826 trial, brentuximab-AVD is being compared with nivolumab-AVD as frontline treatment. Determining the most effective use of these novel treatments is a clear priority, especially since up-front therapy may impact the choice of treatments in the salvage setting.

Sequencing of brentuximab vedotin and anti-PD-1 therapy in relapsed Hodgkin lymphoma remains an open question. The pivotal KEYNOTE-204 study compared brentuximab vedotin with pembrolizumab in patients with relapsed Hodgkin lymphoma (Kuruvilla et al., 2020). Response rates were similar for either treatment, but pembrolizumab therapy resulted in a progression-free survival advantage, prompting some to wonder if this should be positioned before brentuximab vedotin. However, alterations in chromosome 9p24.1 and programmed cell death ligand 1 (PD-L1) expression may impact the effect of anti-PD-1 therapy (Roemer et al., 2016). Again, frontline therapy with brentuximab vedotin in the A-AVD regimen may also influence the selection of salvage therapy.

## COMBINATION THERAPY

More combinations with novel agents are also finding their way into practice. Partnering brentuximab vedotin with well-known salvage regimens like ifosfamide, carboplatin, and etoposide (ICE), dexamethasone, cisplatin, and cytarabine (DHAP), etoposide, methylprednisolone, cisplatin, and cytarabine (ESHAP), or bendamustine leads to PET-negative responses in around 70% or more patients and reasonable progression-free survival based on the reported follow-up (Chen et al., 2015; Garcia-Sanz et al., 2019; Herrera et al., 2018a; Kersten et al., 2020; LaCasce et al., 2018; Moskowitz et al., 2017; Stamatoullas et al., 2019). A study of brentuximab vedotin combined with nivolumab led by Dr. Alex Herrera reports excellent response rates and may be a less toxic lead-in to autologous stem cell transplant (Herrera et al., 2018b). In fact, use of nivolumab monotherapy presents the potential for a chemotherapy-free bridge to autologous stem cell transplant.

### Key Points

- Use of brentuximab vedotin and PD-1 blockade has been associated with improved outcomes in the frontline setting.
- Advanced practitioners are well equipped to assess and manage peripheral neuropathy, as well as monitor and treat for immune-mediated effects.

## NIVOLUMAB MONOTHERAPY

In the NICE study, also led by Dr. Herrera, patients with initial and continued response to monotherapy with nivolumab (nearly two thirds of the 43 included patients) were allowed to proceed to autologous transplant without additional cytotoxic chemotherapy (Herrera et al., 2019a). For those with inadequate response, including progressive disease, ICE chemotherapy was given with nivolumab, which ultimately qualified another 8 of the enrolled patients for autologous transplant.

## KEY ISSUES

Deepening response with PD-1 blockade and avoiding drug resistance with these marquee treatment options are interesting issues being addressed. For example, increased expression of

multidrug resistance (MDR) transporter may confer resistance to brentuximab (Chen et al., 2020). Use of cyclosporine A can inhibit MDR transport; in a phase I study, this approach demonstrated responses in 75% of the 14 brentuximab-refractory patients, but with some increase in toxicity compared with brentuximab alone. Epigenetic modifiers, decitabine and vorinostat, have been investigated to overcome resistance to PD-1 blockade by restoring tumor immunogenicity and reducing T-cell exhaustion (Herrera et al., 2019b; Nie et al., 2019). Not only can adjunctive therapy with decitabine overcome resistance, but use of this agent or the CD30-targeting bispecific antibody AFM13 may actually deepen responses. In landmark studies with either nivolumab or pembrolizumab, we know that patients with complete response are afforded significantly better long-term outcomes (Bartlett et al., 2020).

## OTHER AGENTS UNDER INVESTIGATION

Refining the use of brentuximab vedotin and anti-PD-1 checkpoint inhibitors is not the only active area of research in relapsed Hodgkin lymphoma. Camidanlumab (Cami, ADCT-301) is a CD25-directed antibody-drug conjugate with impressive response rates that appear to be dose related (Hamadani et al., 2018). Drawbacks include a 6.5% incidence of Guillain-Barré syndrome along with liver function test abnormalities, rash, and edema/effusions in 39%, 65%, and 25% of patients, respectively.

It is also no surprise that, based on the application of this platform to other lymphomas, chimeric antigen receptor (CAR) T cells have been developed to treat Hodgkin lymphoma. Use of a CD30-directed CAR T-cell product in the RELY-30 study produced complete or partial responses in 62% of the 42 patients studied, the majority of whom had received prior brentuximab vedotin and/or anti-PD-1 therapy (Ramos et al., 2020). Despite the limited number of patients treated to date, these were primarily heavily pretreated patients, which makes this a very attractive option for further investigation. ●

### The Advanced Practitioner Perspective

Novel agents remain in the spotlight for the management of relapsed Hodgkin lymphoma. Advanced practitioners are well positioned to care for these patients, whether it is providing education on the available options, discussing the benefits and risks of each, or managing potential adverse effects. Assessment and management of peripheral neuropathy, one of the principle adverse effects of brentuximab

vedotin, is built into the skill set of the advanced practitioner since this is an issue that is not unique to this medication. Implementing appropriate monitoring and treatment for immune-mediated effects from checkpoint inhibitors has also become easier with the publication of comprehensive guidelines by the American Society of Clinical Oncology.

### Disclosure

Dr. Valla has no conflicts of interest to disclose.

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