

A Report on a 2014 Clinical Roundtable Monograph: Managing Risk in Hodgkin Lymphoma

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More than 20,000 physicians, scientists, and other professionals specializing in hematology gathered in San Francisco last December for the 56th American Society of Hematology (ASH) Annual Meeting and Exposition. Participants had the opportunity to meet with peers from around the world to discuss the implications of new research and learn more about promising treatment options for patients with various hematologic diseases, including Hodgkin lymphoma (HL). During the Congress, a panel of HL experts was asked to provide their perspectives on some of the emerging clinical data presented at ASH, as well as discuss their therapeutic approaches for managing risk in HL patients. Their reports were captured in the recently published clinical roundtable monograph *Management Risk in Hodgkin Lymphoma*, which can be found in *Clinical Advances in Hematology & Oncology*.¹

To help clinicians better understand and apply emerging data regarding the clinical management of patients with HL, panel members—James Armitage, MD; Robert Chen, MD; Craig Moskowitz, MD; and John Sweetenham, MD—were asked to discuss how new data presented at ASH will affect clinical practice now and in the near future. The four experts focused on what is being done to treat patients with high-risk, advanced-stage HL, because, despite the incredible success rate in treating patients with limited-stage HL (up to 90% of patients are cured),² better treatment options are needed for those patients who have advanced-stage disease or who have relapsed/refractory (r/r) disease. Their reports cover a wide range of topics, including frontline management of high-risk patients, treatment of r/r HL, new frontiers in managing HL, and the impact of the AETHERA trial on clinical practice.

The experts agreed that one of the most exciting aspects of ASH was the release of data regarding novel agents such as antibody drug conjugates, histone deacetylase inhibitors, mammalian target of rapamycin inhibitors, and Janus kinase inhibitors, as well as programmed cell death (PD-1) inhibitors. The four experts discussed what they saw as the most interesting data that relate to treatment of patients with high-risk disease. They also discussed learnings from treating high-risk patients that may be useful in treating early stage, lower-risk patients with therapy that may achieve the same high success rate, but with less toxicity. For instance, brentuximab vedotin was shown to be very active in r/r HL, and trial data highlighted its efficacy in numerous situations, including as consolidation therapy posttransplant in patients at high risk for relapse and as first-line salvage therapy in r/r HL in a neoadjuvant setting in autologous stem cell transplantation (ASCT).

In his chapter on “Frontline Management of Hodgkin Lymphoma Patients with High Risk Disease,” James O. Armitage, MD, professor, University of Nebraska Medical Center, discussed the basics of HL, including a brief history of the discovery of the disease, disease staging, and early treatment options. He then outlines treatment options in the modern era, including ABVD (Adriamycin, bleomycin, vinblastine, and dacarbazine)³ and BEACOPP (bleomycin, etoposide, Adriamycin, cyclophosphamide, Oncovin, procarbazine, and prednisone),³ and goes on to discuss some of the new management approaches that were presented at ASH 2014, including brentuximab vedotin and PD-1 inhibitors.

Dr. Armitage explained that in an earlier phase 2 trial, brentuximab vedotin was found to be very active in r/r HL, with an overall response rate of 75% and a complete remission rate of 34%.⁴ Furthermore, although the drug was not associated with a high cure rate, it allowed patients with r/r disease to proceed to transplantation. That success led to a phase 1 trial of the drug in combination with ABVD and AVD (without bleomycin) in the frontline setting, in which complete remission rates reached 96%.⁵

At ASH 2014, sequential therapy was examined in a pilot phase 2 study that enrolled 12 treatment-naïve HL patients and studied the use of brentuximab vedotin followed by ABVD, with or without radiotherapy. The complete response rate was 83%, and toxicity was limited. Dr. Armitage also discussed new data that suggest that PD-1 inhibitors may have importance in r/r HL and highlighted one trial with a response rate of 87% and a 24-week progression-free survival of 86% in these patients (including patients for whom brentuximab vedotin had failed).⁶

In the second chapter of the monograph “Treatment of Relapsed/Refractory Hodgkin Lymphoma,” Robert W. Chen, MD, assistant professor, Department of Hematology and Hematopoietic Cell Transplantation, City of Hope, discussed treatment of r/r HL and various options for managing patients who are refractory to ABVD. He highlighted that the current follow-up for these patients—ICE (ifosfamide, carboplatin, and etoposide⁷) or DHAP (dexamethasone, cisplatin, and cytarabine)⁸—has significant toxicity (eg, myelosuppression) that can decrease the success rate of ASCT.⁹

At ASH 2014, Dr. Chen reported on results from a phase 2 trial he is currently conducting using single-agent brentuximab vedotin as first-line salvage therapy in r/r HL patients (nearly all of whom failed ABVD) prior to ASCT.¹⁰ Among patients who received brentuximab vedotin alone, the complete response rate was 36%, and the overall response rate was 69%; about half of the patients proceeded to transplantation without needing any additional salvage chemotherapy. Dr. Chen stated that, “Our trial showed that brentuximab vedotin was associated with a high response rate and minimal toxicity.”

In the third chapter of the monograph, Craig H. Moskowitz, MD, professor of medicine, Weill Medical College of Cornell University, described “New Frontiers in the Management of Hodgkin Lymphoma.” His main point was to ask the question, “Can all HL patients can be cured?” With that as a starting point, Dr. Moskowitz discussed the five main risk groups based on the Deauville Criteria¹¹ and the treatment selections based on each group. He described radiation as the “single most effective single agent” treatment for HL, but said that its role continues to diminish as more novel treatments get approval, as well as how positron emission tomography (PET) imaging is being used both as a management component in untreated patients and in the pretransplant setting. He also discussed how brentuximab vedotin and the PD-1 checkpoint inhibitors are emerging as viable treatment options, and described their potential role in a near-future treatment armamentarium.

The data that Dr. Moskowitz cited were results of a phase 1B/2 study combining brentuximab vedotin with bendamustine.¹² As reported by the principal investigator, the complete response rate was more than 80%, and many of the patients proceeded to transplantation. Regarding safety, the combination appeared to be well tolerated, with the exception of a high rate of infusion-related reactions, which led to a subsequent protocol amendment requiring premedication with corticosteroids and antihistamines. The ASH 2014 meeting also included presentations on two of the novel PD-1 inhibitors: nivolumab^{13, 14} and pembrolizumab.¹⁵ The paper briefly explains that these early trials showed that between 80% and 90% of patients achieved clinical benefit from these treatments. The complete response rates ranged from 20% to 30%, and the partial response rates ranged from 30% to 45%. Many of these patients attained prolonged stable disease, and others still have ongoing responses.

Concluding the monograph was John Sweetenham, MD, professor of medicine, Huntsman Cancer Institute, University of Utah. He wrote about, “The Impact of the AETHERA Trial on Clinical Practice” and also wrote a Q&A on recent management considerations in HL. Dr. Sweetenham explained that, in 2009, the AETHERA study group designed a placebo-controlled, random-assignment trial in HL aimed at determining whether patients at risk for relapse after ASCT would benefit from the addition of consolidation therapy with brentuximab vedotin.¹⁶ The study found that 65% of patients who received brentuximab vedotin in the posttransplant setting were progression-free at 2 years, compared with 45% who received placebo.

As discussed previously, although the success rate of treating patients with limited-stage HL with primary chemotherapy or combined modality therapy is around 90%, the AETHERA trial addressed an idea that has recently evolved: the chance of identifying patients at higher risk of relapse after ASCT and offering them posttransplant therapy that could have a substantial impact on their clinical outcome. Dr. Sweetenham speculated that “these results will influence

the management of patients with Hodgkin lymphoma who receive high-dose therapy and undergo ASCT” and probably will lead many oncologists to use a consolidative strategy involving brentuximab vedotin.

To conclude, the 2014 ASH Meeting and Exposition yielded many exciting reports in HL and many other hematologic malignancies. With the speed of scientific discovery we see today, it’s safe to say that ASH 2015, being held in Orlando, Florida, December 5-8, 2015, will offer even more.

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