Moderator: Welcome to Managing Hodgkin Lymphoma With Antibody–Drug Conjugates, a three-part podcast series presented by the publishers of the *Journal of the Advanced Practitioner in Oncology* and Harborside Medical Education. This certified educational podcast is supported by an unrestricted educational grant from Seattle Genetics, Inc. Please visit advancedpractitioner.com to view faculty disclosure information.

Ms. Goodrich: I'm Amy Goodrich, a nurse practitioner and research associate at the Johns Hopkins School of Medicine and the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. I'm joined today by Dr. Nadia Khan, a medical oncologist at Fox Chase Cancer Center. Thanks for joining us.

Ms. Goodrich: Today, Dr. Khan and I will be discussing the role of antibody–drug conjugates in classical Hodgkin lymphoma, including mechanism of action, recent approvals, emerging data, and expert guidance on clinical application for patients with classical Hodgkin lymphoma.

Ms. Goodrich: First, we're going to start with a brief overview of current standard of care. For initial therapy, ABVD still remains a very commonly used regimen. Stanford V is another initial therapy option, as well as BEACOPP, and we are going to talk a little bit more later about brentuximab vedotin plus AVD. And then always with initial therapy, involved site radiation therapy is also commonly used depending upon the patient's stage or specific patient characteristics.

Ms. Goodrich: Then in our relapsed/refractory population, chemotherapy is still prevalent in terms of lymphoma salvage regimens such as DHAP and ESHAP and ICE, gemcitabine-based regimens, bendamustine, things like C-MOPP and brentuximab vedotin is there as something a little more interesting than chemotherapy, as well as small molecule agents that have relatively recently come to our guidelines. Things like everolimus and lenalidomide, and then even more recently our checkpoint inhibitors, nivolumab and pembrolizumab.

Ms. Goodrich: So when thinking specifically about anti-CD30 antibody–drug conjugates, in thinking about the mechanism of action, Dr. Khan, do you want to talk a little bit about these antibody–drug conjugates?

Dr. Khan: The mechanism for brentuximab vedotin really represented a new way of a therapeutic approach for lymphomas and specifically Hodgkin lymphoma, as well as anaplastic large cell lymphoma. The antibody part of the therapy targets CD30, which is a protein expressed on the majority of Reed-Sternberg cells. Those are the malignant cells in Hodgkin lymphoma, and the antibody is linked to a toxic molecule, MMAE. When the antibody binds to the Reed-Sternberg cell, the toxin is delivered to the lymphoma cell. And once it's internalized, it binds to tubulin, and this leads to a mitotic arrest or apoptosis or cell death of the cancer cell.

Ms. Goodrich: Thank you. Alright. Next, let's talk about brentuximab vedotin in the relapsed/refractory classical Hodgkin setting. If you remember, it was approved in 2011 as monotherapy, and the majority of those patients had received an autologous transplant and had received two or more lines of therapy. The overall response rate was 73% with modified progression-free survival at 6.7 months. Why were those results so clinically significant at that time?

Dr. Khan: Although the cure rate for patients with Hodgkin lymphoma after having received first-line therapy is very high, with 90% of patients rendered disease free, relapsed and refractory disease of our patients still remains a major challenge. The approval of brentuximab vedotin was a major breakthrough because it was the first targeted therapy made available for Hodgkin lymphoma patients, where historically we've had chemotherapies available as the mainstay of therapy.

Dr. Khan: Autologous transplant is considered the standard of care for relapsed/refractory Hodgkin lymphoma that is considered to be chemotherapy sensitive. The use of novel agents to replace chemotherapy in the relapsed/refractory setting is being evaluated in clinical trial only at this time. Chemotherapy-based salvage regimens can achieve impressive response rates in the range of 70 to 90% of patients with relapsed/refractory Hodgkin lymphoma.

Dr. Khan: Platinum-based regimens such as ICE chemotherapy or DHAP chemotherapies are typically used in the salvage setting. Additionally, gemcitabine-based regimens such as GemOx or GDP and bendamustine regimens have resulted in high response rates. Bendamustine as a single agent can achieve an overall response rate of 50%.

Dr. Khan: BeGEV is a notable bendamustine-containing regimen, which includes bendamustine, gemcitabine, vinorelbine. There was a multicenter, phase 2 study of 59 patients with relapsed/refractory Hodgkin lymphoma, and an overall response rate of 83% was achieved, with 73% of patients having achieved a complete response. The common grade 3 or 4 adverse events in this study were febrile neutropenia, infections, thrombocytopenia, and neutropenia.

Dr. Khan: In the pivotal phase 2 trial of BV in 100 patients that you referred to previously, Amy, in patients with relapsed/refractory Hodgkin lymphoma, the overall response rate was similarly impressive with 75% of patients having achieved a response, and 34% of those patients with a complete response. A maximum of 16 cycles was offered in this trial, and remember, these are high-risk patients. These are patients who've received an autologous bone marrow transplant. A long-term follow-up analysis showed that 47% of patients were still alive at 3 years, and for the 34 patients on the study who had a complete response, the 3-year progression-free survival was 58%, with an overall survival of 73%.

Dr. Khan: Remarkably, 47% of patients who achieved a complete response were still in remission at a follow-up a 53 months. And of 16 patients who remained in remission long term, four ended up having an allogeneic transplant in complete

response, and 12 patients did not have any subsequent therapy yet remained in a CR. Given the durability of the responses and complete responses in some patients that were very durable, this has prompted evaluations with chemotherapy combination with brentuximab vedotin, and this is now being introduced in earlier lines of therapy and is undergoing evaluation in clinical trials as well.

Dr. Khan: The NCCN guidelines outline BV chemotherapy combinations for consideration in the relapsed/refractory setting, including BV with ICE, BV with ESHAP, and others. So within the context of relapsed/refractory disease prior to autologous bone marrow transplant, patients may be considered for chemotherapy or BV chemotherapy combinations.

Ms. Goodrich: Great, thank you. So to talk a little bit about checkpoint inhibitors, where do they fit into your typical treatment paradigm, and how do they influence the use of BV in the relapsed/refractory setting?

Dr. Khan: The checkpoint inhibitors nivolumab and pembrolizumab are both FDA approved for multiply relapsed Hodgkin lymphoma. Nivolumab's approval is specific for patients having received an autologous bone marrow transplant and after treatment with brentuximab vedotin, and pembrolizumab similarly is approved for patients who have received three lines of prior therapy with relapsed/refractory disease.

Dr. Khan: High response rates have been seen with both therapies in these settings. A phase 1 study of nivolumab in 23 patients with relapsed/refractory Hodgkin lymphoma showed an 87% response rate, with 17% complete responses. An 80-patient phase 2 CheckMate study of single-agent nivolumab reported an overall response rate of about 66%, with 9% having achieved complete response. Longer follow-up remission durations seem to have improved from about 8 months to 13 months. Response rates are similarly impressive for single-agent pembrolizumab, and most of the toxicity seen with either of these drugs are immune related.

Dr. Khan: Overall, I would say that checkpoint inhibitors are an excellent option for patients who relapsed after having received an autologous bone marrow transplant and BV therapy. Ongoing studies combining checkpoint inhibitors with chemotherapies and brentuximab vedotin in the post-transplant setting are ongoing, and the results seen so far are very promising.

Ms. Goodrich: Well, thank you. It's certainly a great outlook for patients who are not cured with their initial therapy. The next study that I want to talk to is the AETHERA study, which was a placebo-controlled, phase 3 study of BV post-autologous transplant versus placebo post-autologous transplant. Patients were transplanted and they were randomized to either receive BV or receive placebo, and the progression-free survival for the patients who have who received BV was 43 months versus 24 months for the placebo folks. Similarly the 5-year progression-survival for the BV arm was 59% versus 41 for placebo. So do you

want to talk a little bit about this study, and who were the patients who we fleshed out, were most likely to benefit from this therapy? Just your thoughts on this approach in general?

Dr. Khan: BV following autologous transplant as an adjuvant therapy or maintenance therapy in high-risk patients is an approved indication based on the results of this AETHERA trial. The high-risk patients who were eligible for this study included those who did not achieve a complete response to first-line therapy, those patients who progressed within a year of initial therapy, and those patients who had relapsed at extranodal sites.

Dr. Khan: The median progression-free survival for these patients who received adjuvant BV was about 43 months, versus 24 months in patients who were only observed after autologous transplant. There was no difference in overall survival, and a third of patients, importantly, discontinued the adjuvant BV because of adverse events encountered—most commonly neuropathy and neutropenia. Even though there was no overall survival advantage, seeing the ability to delay the time to next treatment or transplant is a clinically meaningful outcome for many young patients with diminishing treatment options after having relapsed disease following autologous bone marrow transplant.

Dr. Khan: I believe that BV as a maintenance or adjuvant after autologous transplant is a worthwhile consideration in high-risk patients who have few remaining options. And it's important to consider their prior toxicity history in patients who've experienced neuropathy or significant rash with potentially BV even prior to autologous transplant. It may be worthwhile to delay BV maintenance, and in many cases, we have waited for patients to relapsed before initiating their next line of therapy.

Ms. Goodrich: Okay, and then just to wrap up this study, so we talked about progression-free survival being superior in the group that received BV, and there's an overall survival evaluation plan for 2020. Can you talk about what that will mean for this study and the use of BV post-transplant?

Dr. Khan: Even absent an overall survival advantage with BV maintenance, it's very appropriate to still consider the regimen for a PFS advantage. Again, because patients in this setting often have few therapies available to them and often are looking forward to a next therapy of allogeneic transplant, which does subject patients to significant toxicities and potentially would impact quality of life. Enabling patients to continue on a well-tolerated regimen such as BV in some cases would prolong their next therapy and potentially would prolong the time to allogeneic transplant, which for a young patient would be advantageous.

Ms. Goodrich: So the next study we're going to look at is the ECHELON-1 trial, and the ECHELON-1 trial looked at ABVD, which is our historic gold standard, versus BV plus AVD, so trading the bleomycin in ABVD for brentuximab vedotin in untreated advanced-stage classical Hodgkin lymphoma patients. So looking at 2-year data, the modified progression-free survival with the BV AVD arm was

82.1% versus 77.2% with ABVD. Based on these data, this brentuximab vedotin plus AVD was approved in March of 2018 for use in advanced Hodgkin lymphoma as initial therapy. So how important is this 4.9% improvement in progression-free survival?

Dr. Khan: The roughly 5% advantage in the progression-free survival with BV chemo paired with ABVD is modest considering the significant toxicities associated with the combination. Many practitioners rely on the RATHL data to inform treatments based on interim PET scan, which allows most patients, approximately 80%, to continue on with AVD therapy for remaining cycles.

Dr. Khan: While we don't have a head-to-head comparison of AAVD to AVD, it is likely that most patients would achieve a complete response with fewer therapies and improved toxicity profile as per the RATHL paradigm.

Ms. Goodrich: Okay. You talked a little bit about the side effect profile with the BV AVD, and just to talk about that a little more, there were higher rates of febrile neutropenia and peripheral neuropathy, all sorts of GI toxicities. There were more serious adverse events, there were more hospitalizations. And the addition of growth factor to the BV AVD arm reduced febrile neutropenia, and peripheral neuropathy was managed by dose modifications. Given the modest progression-free survival improvement and the increased toxicity profile, who are the patients who are most appropriate for initial therapy with brentuximab vedotin plus AVD?

Dr. Khan: That's a good question, and I would say that patients who are unable to receive bleomycin as a result of pulmonary comorbidities or advanced age would be very appropriate candidates for the ECHELON treatment plan. And while there are significant toxicities associated with the regimen, as you mentioned, use of growth factor is now considered a mandatory part of the treatment, and hopefully febrile neutropenia would be significantly reduced with institution of colony-stimulating factors.

Ms. Goodrich: Great. To wrap up the ECHELON-1 study, there are value-based considerations here, including not only the price of brentuximab vedotin, but also the financial and personal cost of the higher adverse events and more intensive supportive care required. But as you stated, there certainly are patients we just don't want to use bleomycin in, and this certainly offers them a nice option.

Dr. Khan: Absolutely. The results of the ECHELON study were reassuring in that the PFS was slightly better than the comparison arm of ABVD. However, it's a regimen that could be beneficial in those select patients that we've outlined who would otherwise not be candidates for bleomycin.

Ms. Goodrich: Yes. That's wonderful. So do you want to talk a little bit, before we wrap up, about the role of biomarkers in classical Hodgkin lymphoma? I know in many of

our diseases, we're very biomarker focused. So do you want to give us an update in what's happening in classical Hodgkin lymphoma?

Dr. Khan: There are a number of potential biomarkers that appear promising and may correlate with outcomes and risk for eventual relapse. There are currently no integral or integrated biomarkers that are a part of our standard of care. The biomarkers that are being evaluated in large prospective clinical trials including a SWOG-led Alliance study, includes the use of circulating tumor DNA correlated with interim PET results and immune markers such as MHC class I and class II as it relates to sensitivity to checkpoint inhibitor therapy.

Dr. Khan: Generally speaking, the biomarkers that are being evaluated are those that describe the characteristics of the Reed-Sternberg cells, those that better characterize the microenvironment surrounding the Hodgkin Reed-Sternberg cells, and third, those that characterize the genetic expression profile of the Reed-Sternberg cells, or those that better define the utility of circulating tumor DNA in patients with Hodgkin lymphoma.

Ms. Goodrich: Okay, so there's no magic biomarker, but lots under study and lots coming, I'm sure. To wrap up, our PEARLs or key takeaways today are brentuximab vedotin certainly plays a role in first-line therapy now. It plays a role in maintenance therapy, post-autologous stem cell transplant, and also in the relapsed/refractory setting. Its newest indication is first line with BV plus AVD.

Ms. Goodrich: So what's happening in our classical Hodgkin setting is that more treatment options are wonderful, but it really requires increased attention to careful patient selection based on their risk factors and their comorbidities. Classical Hodgkin lymphoma remains a highly curable disease. Historically, we've had very few treatment options for those not cured with initial therapy, and now we have a growing number of treatment options for those patients.

Ms. Goodrich: I thank you for joining us today, and thank you, Dr. Khan, for this great conversation.