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Raising the Bar for Hodgkin Lymphoma: Optimizing Immunotherapy in Community Practice

Announcer:
Welcome to CME on ReachMD. This activity, titled "Raising the Bar for Hodgkin Lymphoma: Optimizing Immunotherapy in Community Practice," is jointly provided by Medical Education Resources and PleXus Communications.

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Dr. Herrera:
Hello, my name is Alex Herrera, and I'm the Chief of the Division of Lymphoma at City of Hope. Today, we will be discussing how we have raised the bar for Hodgkin lymphoma and how to optimize immunotherapy in community practice.

At the conclusion of this activity, participants should be able to evaluate recent clinical trial results regarding immunotherapy for Hodgkin lymphoma, including frontline and later lines of treatment; propose ways to optimize immunotherapy for Hodgkin lymphoma in the community practice setting based on patient-specific factors, risk stratification, and patients' treatment goals; identify and manage toxicities associated with immunotherapy for Hodgkin lymphoma.

So, just to frame the conversation today, we'll discuss the pathogenesis of classic Hodgkin lymphoma. So, Hodgkin-Reed-Sternberg cells are the tumor cell in Hodgkin lymphoma. Hodgkin-Reed-Sternberg cells are derived from germinal center B cells that have lost their B-cell program, and they don't produce immunoglobulins. There are mutations in the Hodgkin-Reed-Sternberg cells that lead to NF-κB or JAK-STAT pathway activation, and the Reed-Sternberg cells promote immune tolerance, so they kind of create this immunosuppressive microenvironment around them to evade immune attack from a patient's immune system.

Now, we've come to understand that the PD-1 pathway is fundamental to the pathogenesis of classic Hodgkin lymphoma. There are chromosomal alterations in 9p24.1 that are the genes that encode for the PD-1 ligands, and those chromosomal alterations lead to overexpression of the PD-1 ligands in Hodgkin-Reed-Sternberg cells, and that leads to an exquisite sensitivity of Hodgkin lymphoma to PD-1 blockade. That really kind of is the fundamental premise that we're going to talk about throughout the presentation.

So here's an outline of today's presentation. We're going to start by discussing the treatment of early-stage classic Hodgkin lymphoma.

There are several prognostic classification schemes for early-stage Hodgkin lymphoma, and that allows us to determine whether patients have favorable or unfavorable early-stage Hodgkin lymphoma, and that stratifies patients for various treatment regimens.

Now, the German Hodgkin Study Group and the EORTC schemas are the most commonly used. But basically, to summarize, the presence of any one of the following features makes a patient unfavorable, and that's older age for the EORTC criteria, disease bulk, elevated ESR, especially with B symptoms, involvement of extranodal sites in the German Hodgkin Study Group criteria, and the number of sites of involvement in the body.

Now, the fundamental tenets of the treatment of early-stage Hodgkin lymphoma have been either to use combined-modality therapy, combining chemotherapy with radiation, or PET-adapted chemotherapy alone.

Now, the study that has established the combined-modality therapy regimen for early-stage favorable Hodgkin lymphoma is the German Hodgkin Study Group HD10 study. That was a randomized trial, patients with early-stage favorable disease. Patients were randomized to receive different numbers of cycles of ABVD and different doses of radiation. And what we found was that as little as two cycles of ABVD and 20 Gy of involved-field radiotherapy was sufficient to lead to similar outcomes to patients who received the more cycles and higher doses of radiotherapy.

Another important study that has determined how we treat early-stage favorable Hodgkin lymphoma is the H10 EORTC study. And in the H10 favorable cohort, patients were randomized to receive combined-modality therapy, ABVD combined with radiotherapy, or PET-adapted omission of radiotherapy. Now, what we learned from this study was that actually the omission of radiotherapy led to significantly inferior outcomes. The outcomes were still reasonably good, particularly in the young patients that develop Hodgkin lymphoma. It remains a consideration, of course, to omit radiotherapy, but we just have to understand that the outcomes, the progression-free survival, will not be quite as good, but importantly, overall survival was similar.

So, the standard management of early-stage favorable Hodgkin lymphoma, again, is either combined-modality therapy, depending on the German Hodgkin Study Group criteria or whether a patient meets the EORTC criteria. There's a different number of cycles of ABVD with a different dose of radiotherapy. Now, we do have these PET-adapted studies that have omitted radiotherapy, and overall the message was if we omitted radiotherapy, the cure rate with the frontline therapy was a little lower, and we have to understand that. But the overall survival was similar because those patients could be salvaged, and especially in young females who have mediastinal involvement, for example, or axillary involvement, it's a very reasonable thing to consider omission of radiotherapy.

Now, in terms of unfavorable early-stage Hodgkin lymphoma, again, the options are to choose between combined-modality therapy or PET-adapted omission of radiotherapy. The HD11 study from the German Hodgkin Study Group has really established the combined-modality standard for early-stage unfavorable disease. Again, patients were randomized to receive different number of cycles or types of chemotherapy, either ABVD or BEACOPP, and different doses of radiotherapy. Now, importantly, in this study, for unfavorable patients, we did need that higher dose of radiation, 30 Gy, but we could use four cycles of ABVD, and so that's established that standard of four cycles of ABVD with 30 Gy of radiotherapy.

And similarly, in the H10 unfavorable cohort of the EORTC H10 study, patients were randomized to receive four cycles of ABVD with radiotherapy or PET-adapted omission of radiotherapy, but this time a full six cycles of ABVD. And importantly, here there wasn't such a large difference between the arms when you gave patients more cycles of chemotherapy, a full six-cycle course.

Now, the RATHL study confirmed those results in a way. We think about the RATHL study as an advanced-stage Hodgkin lymphoma study, but really nearly 1/2 of the patients had early-stage unfavorable disease, and patients were randomized to receive—if they had a negative PET scan for two cycles of ABVD, they were randomized to receive AVD for four cycles or ABVD for four cycles. And importantly, this study was really evaluating the omission of bleomycin and its noninferiority. Right? Could you omit bleomycin safely since it leads to lung toxicity? And this study did find that. But importantly, in this study, patients who had six cycles of chemotherapy regimen with no radiotherapy, who had stage II disease, had a 3-year progression-free survival of 90%, which is almost identical to what we observed in the H10 unfavorable study.

So again, you know, for unfavorable Hodgkin lymphoma, you know, we've come to understand that you can use combined-modality therapy or a full course of chemotherapy, but that would be six cycles when you omit the radiotherapy.

Now, we've also studied novel agents in early-stage unfavorable disease that includes brentuximab vedotin, and studies of the use of frontline BV in early-stage Hodgkin lymphoma have been promising. The regimens have been well tolerated. They produce excellent progression-free survival, and that's brentuximab vedotin combined with AVD chemotherapy, or even brentuximab vedotin with doxorubicin and dacarbazine with omission of vinblastine, and that omission of vinblastine, of course, led to less peripheral neuropathy.

And the BREACH study was a randomized trial that combined BV-AVD with radiotherapy compared to ABVD plus radiotherapy, and it was a randomized phase 2 study. Complete response rate was the primary endpoint, and BV-AVD plus radiotherapy did lead to a higher end-of-treatment complete response rate, but notably, the progression-free survival was also better when patients received BV-AVD combined with radiotherapy compared to ABVD combined with radiotherapy.

And this has led to BV-AVD being included in our NCCN Guidelines for early-stage unfavorable disease.

Now, the NIVAHL study evaluated nivolumab combined with AVD combined with radiotherapy, and this was a randomized phase 2 study. Now, all the patients on this study received nivolumab either concurrently with AVD followed by radiotherapy or sequentially, nivo alone followed by nivo-AVD, followed by AVD alone, followed by radiotherapy.

The study led to really impressive outcomes when patients received PD-1 blockade as part of their frontline therapy for early-stage

unfavorable Hodgkin lymphoma. The progression-free survival was 100% in the concurrent arm, 98% in the sequential arm, and that led, again, to nivo-AVD being included in the NCCN Guidelines for the treatment of early-stage unfavorable disease.

So, just to summarize, for patients with early-stage unfavorable disease, patients can receive combined-modality therapy, for example, ABVD for four cycles with 30 Gy radiation. They can receive chemotherapy alone, and that would be, for example, ABVD for six cycles with PET-adapted omission of bleomycin, as per the RATHL study. Patients can have the inclusion of novel agents like nivolumab or brentuximab vedotin with chemotherapy. Typically, that would be followed by radiotherapy.

Now, I'll just briefly mention, you know, we've studied novel ways of evaluating the prognosis of early-stage Hodgkin lymphoma, and so we have this E-HIPI score, which is a calculator, and the E-HIPI score looks at traditional risk factors, but as continuous variables, and it's just a more accurate way of prognosticating outcomes in these patients. And there's an online calculator that you can use in the clinic.

We move on to the treatment of advanced-stage Hodgkin lymphoma. The treatment of advanced-stage Hodgkin lymphoma has been primarily systemic chemotherapy alone, as opposed to the use of radiotherapy, but longer courses, full courses of systemic chemo, so six cycles of ABVD.

And as I mentioned, the RATHL study did evaluate PET-adapted omission of bleomycin and showed that that was noninferior to, you know, six cycles of ABVD. So we give two cycles of ABVD followed by four cycles of AVD in patients who have a negative PET scan after two cycles, and, you know, that really established kind of how we treated advanced-stage Hodgkin lymphoma, certainly in North America.

Now, in Europe they've used the BEACOPP regimen. And escalated BEACOPP leads to excellent disease control in advanced-stage Hodgkin lymphoma, really the best disease control that we had observed until recently, with, for example, 5-year estimates of almost 90% PFS in patients who were treated with escalated BEACOPP.

So, for decades, this is how the treatment of Hodgkin lymphoma looked. We could use ABVD. Even though the efficacy was not quite as good as BEACOPP, we were able to salvage patients who relapsed, and so the overall survival was similar. Importantly, with BEACOPP, there were issues with fertility and second cancers down the line, and so there were trade-offs: Better efficacy, but increased long-term toxicities and late effects.

Now, the ECHELON-1 study evaluated brentuximab vedotin incorporated into frontline treatment for advanced Hodgkin lymphoma. Patients with stage III or IV Hodgkin lymphoma were randomized to receive six cycles of ABVD or brentuximab vedotin combined with AVD, and the study demonstrated that the 2-year modified progression-free survival was longer with BV-AVD compared to ABVD. So, the study met its primary endpoints. But importantly, BV-AVD was more toxic than ABVD in adults. There was more peripheral neuropathy. There was more febrile neutropenia, sepsis, and infections, and that required the use of G-CSF as primary prophylaxis. Growth factors were necessary to give with this regimen.

Now, with longer follow-up at 6 years, brentuximab vedotin and AVD was again shown to lead to durable, improved outcomes compared to ABVD from a progression-free survival perspective. But very importantly, at 6 years, we saw an overall survival benefit with brentuximab vedotin AVD, and that really kind of led to, I think, most people adapting their practice.

So, as of just a few years ago, this is how the treatment of Hodgkin lymphoma looked like in advanced-stage disease. We used ABVD or escalated BEACOPP, but now we had brentuximab vedotin AVD as an option.

So, we'll now talk about the incorporation of frontline immunotherapy for advanced-stage Hodgkin lymphoma. So, I mentioned BV-AVD had become a standard for advanced-stage Hodgkin lymphoma. And so, you know, with this understanding that PD-1 was so important to the pathogenesis of this disease, and with early studies starting to show promising results in relapsed/refractory disease, and ultimately even some smaller studies in the frontline setting using PD-1 blockade, we took on this question of whether or not we could introduce PD-1 blockade into the frontline setting for the treatment of advanced-stage Hodgkin lymphoma.

So, we designed SWOG S1826. It's a randomized phase 3 study. Patients with stage III or IV Hodgkin lymphoma were randomized to receive nivolumab combined with AVD for six cycles or brentuximab vedotin combined with AVD for six cycles. G-CSF was required in the BV arm; it was optional in the nivolumab arm. Patients were allowed to receive end-of-treatment radiotherapy to residually FDG-avid lesions. That had been an important standard in pediatric patients, and so because this study was a collaboration with the Children's Oncology Group, and we enrolled patients as young as 12 with no upper age limit, we did allow the radiotherapy.

The primary endpoint of the study was progression-free survival. Key secondary endpoints are listed here on the slide, including overall survival. Patients are stratified by age, International Prognostic Score, and the intent to use radiotherapy. So, the baseline characteristics of patients enrolled to S1826 are shown here. As I mentioned, adolescent patients were eligible to be enrolled on the

study and comprised 1/4 of patients on the study. We also enrolled older patients because we weren't using BEACOPP or its variants. So, the baseline characteristics of patients enrolled to the S1826 study are shown here. About 1/4 of patients were under the age of 18. As I mentioned, we did allow the enrollment of adolescents onto the trial, and about 10% of the patients were over the age of 60, 1/4 of patients were Black or Hispanic, and nearly 2/3 of patients had stage IV disease. We did allow the enrollment of patients with HIV onto the study, so overall, this was a very representative study, inclusive of high-risk patients.

S1826 met its primary endpoint. Nivolumab-AVD improved progression-free survival compared to BV-AVD, with a 2-year progression-free survival of 92% with nivo-AVD compared to 83% with BV-AVD, and there were nearly twice the number of progression or death events in the BV arm. As you can see here in this forest plot, the benefit associated with nivolumab-AVD from a progression-free survival standpoint was consistent across subgroups. So older patients, younger patients, high IPS score, low IPS score, stage III or stage IV, patients in all these different subgroups benefited from nivolumab-AVD.

Now, this past year at the ASH Annual Meeting, we provided an update and we showed that the 3-year progression-free survival in the S1826 study was 91% in patients who received nivo-AVD compared to 82% in patients who received brentuximab vedotin AVD, really confirming that the benefit was sustained at 3 years of follow-up.

Now, importantly, S1826 demonstrated that nivolumab combined with AVD was better tolerated than brentuximab AVD. There were fewer patients who had peripheral neuropathy in the nivolumab arm, a lot more neuropathy in the BV arm. There was actually more neutropenia in the nivo arm, but that's because G-CSF was not required. This is similar to the old days of ABVD, where all patients are basically going to have neutropenia. But what we showed is that there was not a functional consequence of that increased neutropenia. So, the rates of febrile neutropenia or sepsis and infections were not increased in the nivo arm. Of course, there were immune-related adverse events that we did observe in the nivolumab arm, but they actually were not terribly dissimilar from what we observed in the BV arm. So, there wasn't a high rate of immune-related adverse events.

So, the treatment disposition in the S1826 study is shown here. There were more patients who had to discontinue treatment in the BV arm, and that was either due to progression, relapse, or death, or just treatment discontinuation altogether. Up to 22% of patients had to discontinue the BV compared to 9% of patients who had to discontinue the nivo, and 27% of patients had dose reduction of brentuximab vedotin.

Importantly, I mentioned that patients were allowed to receive radiation on this study, but less than 1% of patients received radiotherapy, and that's a huge change from the prior standard of care in adolescent patients. Normally, according to pediatric protocols that were used previously, up to 60% of patients would have received radiotherapy, so this was a massive decrease in the amount of radiotherapy that patients received.

Now, in terms of the overall survival, these data are not yet mature. The overall survival was similar, although there were twice the number of deaths in the BV arm.

Now, while we were kind of improving on the ABVD backbone with brentuximab vedotin first, and then ultimately with nivolumab, in Europe, the German Hodgkin Study Group was improving on escalated BEACOPP. The HD21 study evaluated BrECADD, which was a regimen that incorporated brentuximab vedotin into escalated BEACOPP with omission of procarbazine and some other modifications to the chemotherapy to try to make the frontline treatment better tolerated. This was a PET-adapted study. Patients were randomized to receive BEACOPP or BrECADD, and then based on the results of the interim PET scan after two cycles, they would receive either fewer or more cycles of one of the regimens.

This slide just shows how BEACOPP was remodeled. Again, we incorporated brentuximab. Vincristine was dropped. Dacarbazine was substituted for procarbazine, and so the intent here was to have less gonadal toxicity to improve long-term fertility and fewer second malignancies.

So, not surprisingly, HD21 showed that BrECADD was better tolerated than escalated BEACOPP, as you can see here in this slide, and actually the study was designed as a noninferiority study from an efficacy perspective. But in fact, BrECADD was superior to escalated BEACOPP, and the PFS at 5 years with BrECADD was 94% compared to 91% with escalated BEACOPP. Really, a remarkable result, given that the efficacy with escalated BEACOPP was so excellent. And as hoped, the long-term kind of fertility outcomes and gonadal function was improved with BrECADD as compared to escalated BEACOPP.

So, this is now how the management of advanced Hodgkin lymphoma looks. We have nivolumab-AVD as the kind of most effective regimen in the ABVD lineage, and BrECADD as the most effective regimen in the BEACOPP lineage, and these two are the most effective options for the treatment of advanced-stage Hodgkin lymphoma, with other regimens like BV-AVD or ABVD useful in certain circumstances.

Now, I mentioned the E-HIPI. We also have the A-HIPI, which is a novel prognostic score in advanced-stage disease, and we have shown that the A-HIPI performs better than the traditional IPS score for prognosticating in patients who receive modern therapies.

We also have studied circulating tumor DNA in patients with advanced-stage Hodgkin lymphoma, and this is a little bit of a future directions where, you know, we've now achieved excellent outcomes, you know, both with ABVD-based backbones and escalated BEACOPP, but perhaps we can incorporate ctDNA as a way to adapt or optimize therapy. And in this study, you could see the 3-year PFS in patients who were ctDNA negative at interim was excellent and much better than patients who had detectable ctDNA after two cycles. And you can compare, for example, a PET to ctDNA and really see that the ctDNA outperformed PET as a way of detecting residual disease, though there was some benefit of having both. So, hopefully in the future we can incorporate ctDNA to continue to improve on our therapies.

So we'll start off with a case. Mr. Adams is a 22-year-old man who presented with a 7-week history of pruritus, fatigue, fevers, night sweats, and a neck mass. He had palpable cervical and axillary lymphadenopathy. His labs showed some anemia, low albumin, elevated white count. A PET demonstrated multistation lymphadenopathy, also with bony FDG-avid lesions, and a lymph node biopsy confirms a diagnosis of nodular sclerosis Hodgkin lymphoma. So, given these options, what would be your next step in managing the patient? And the options are PET-adapted ABVD as per the RATHL study, brentuximab vedotin AVD for six cycles, nivolumab AVD for six cycles, combined-modality therapy with ABVD and radiation, or brentuximab vedotin and nivolumab for six cycles.

Now here, based on the S1826 study, nivolumab AVD represents the most effective option for a patient with advanced-stage Hodgkin lymphoma. Outcomes were improved, and the regimen was better tolerated compared to brentuximab vedotin AVD. And we discussed that for patients with advanced-stage disease, they need a full course of systemic therapy. So combined-modality therapy with only four cycles of ABVD is not the right option. And BV plus nivolumab alone for only six cycles has not been shown to be as effective as a full course of immunotherapy combined with chemotherapy.

Now, I'll briefly discuss the management of treating older patients with Hodgkin lymphoma. This has really been a challenge over the years. There is a late peak of incidence of Hodgkin lymphoma in older patients, and we see that these patients actually have poor tolerance of chemotherapy due to comorbidities and frailty. They have increased risk of bleomycin lung toxicity that impacts the treatment delivery, and so their outcomes have traditionally been poorer than younger patients with this disease.

What we found in the S1826 study was that nivolumab AVD prolonged progression-free survival quite remarkably in older adults. The 3-year PFS was 82% with nivo-AVD compared to only 58% with BV-AVD. And importantly, we understood that BV-AVD was toxic and really should be avoided in older adults. There were multiple deaths on the study. It was very poorly tolerated. So combining brentuximab with AVD should not be given in adults over the age of 60.

Now, in a patient that does need to receive BV combined with AVD, so for example, a patient with an autoimmune disease in whom you're not going to want to give nivo-AVD, but they can tolerate anthracycline-containing chemotherapy, you can use sequential BV followed by AVD. So, brentuximab alone for two cycles, then sequential AVD without the brentuximab, and then going back to the BV, and that has led to excellent outcomes with a 2-year PFS of 84% in a multicenter study conducted by Andy Evens.

Now, in patients who cannot tolerate chemotherapy, you can use brentuximab vedotin-based doublets. So, for example, BV with dacarbazine or BV combined with nivolumab, and that has led to some durable responses in patients and quite a high response rate. So at least you can get disease control and give patients some time of disease control.

Let's discuss another case. This is Mrs. Brown, a 74-year-old female with weight loss and a new neck mass. The patient has an elevated white count and reasonable performance status. There's multistation lymphadenopathy above and below the diaphragm with splenomegaly, consistent with stage III disease. No disease bulk, and a biopsy confirms mixed-cellularity Hodgkin lymphoma that is EBV positive, so advanced-stage EBV-positive Hodgkin lymphoma in an older adult. And so, which of the following options would be the best step for managing this patient? Nivo-AVD for six cycles, BV combined with AVD for six cycles, RATHL approach with six cycles of PET-adapted ABVD, escalated BEACOPP, or BrECADD?

Again, the answer would be nivo-AVD based on the outcomes observed in the S1826 study in older patients. We know that BV combined with AVD is too toxic for older patients. Escalated BEACOPP is certainly too toxic for older patients, as is BrECADD. Unfortunately, outcomes in older patients with BrECADD have shown, you know, quite a bit of toxicity. So, and you'd want to avoid bleomycin in older patients. So, ABVD is also not the right answer.

So, you know, in terms of the factors that affect treatment decisions, you know, there are some important things to consider whether or not you should use nivolumab in a patient with Hodgkin lymphoma. Of course, I started to mention autoimmune disease as probably a reason that you would not want to use nivolumab, and in that case, you'd probably think about using a brentuximab vedotin-based

regimen, and I've listed some others here on this slide.

So let's move on to relapsed/refractory disease. You know, the standard treatment of relapsed/refractory disease in Hodgkin lymphoma is salvage therapy followed by autologous stem cell transplant in patients who are sensitive to treatment. Historically, we've used chemotherapy, and some chemotherapy regimens are listed here on the slide. We usually got to a complete response by PET in just over 1/2 of patients, and then patients who proceeded to autologous stem cell transplant were cured about 1/2 of the time.

We'd started to study brentuximab vedotin in the relapsed/refractory setting and understood that in patients who had progressed after an autologous stem cell transplant, BV led to a complete response about 1/3 of the time, and about 10 to 20% of patients actually could achieve durable complete response.

Now, PD-1 blockade was studied in a similar setting at first. Patients who had progressed after brentuximab vedotin and/or autologous stem cell transplant, most patients again responded. About 1/4 of patients had a complete response. If a patient got into complete response, about 1/2 of those patients remained in a complete response long term, although that was a minority in total.

Now, in the relapsed/refractory setting, a randomized phase 3 study, the KEYNOTE-204 study, showed that PD-1 blockade leads to longer progression-free survival than brentuximab. So, in terms of sequencing, it was clear that we should use PD-1 blockade ahead of BV.

And I won't take you through every study using BV and PD-1 blockade in the salvage setting, but many regimens were evaluated, and what we found is that BV did increase the CR rate and the progression-free survival rate compared to traditional chemotherapy and transplant alone. But really, when you included PD-1 blockade into the salvage regimen, there was really unprecedented high complete response rates, upwards of 85-90%, and incredible progression-free survival when PD-1 blockade was used in salvage, and patients went on to autologous stem cell transplant, again with PFS higher than 80-90%. So that really established PD-1 blockade as part of salvage therapy, and multiple studies have now confirmed that. We've never done a randomized study. But these are all retrospective studies showing that when you use PD-1 blockade as part of your salvage, even if you only look at patients who are in a complete response at the time of their autologous stem cell transplant, patients who received PD-1 blockade as part of their salvage had better outcomes, as you can see here in this study that was published in *Blood* this past year.

We'll move on to the consolidation after transplant setting. The AETHERA study demonstrated that BV consolidation led to improved progression-free survival compared to placebo alone in high-risk patients. Five-year PFS was 59% with BV and 41% in patients who did not receive BV. So, that really established BV consolidation as an option for high-risk patients after autologous stem cell transplant. Now, importantly, patients treated on the AETHERA study were naive to BV.

We have also studied PD-1 blockade as consolidation after autologous stem cell transplant. We've studied pembrolizumab in a small phase 2 study, and those patients who received pembro had great outcomes, although there was some immune-related toxicity that we did observe.

We've also studied BV combined with nivo as post-transplant consolidation in high-risk patients with relapsed/refractory Hodgkin lymphoma. Again, the outcomes were really fantastic, with more than 90% progression-free survival.

Let's talk about Mrs. Williams. This is a 30-year-old woman diagnosed with stage IV Hodgkin lymphoma who received BV-AVD as her frontline therapy, achieved a complete response, and then 7 months later relapsed with fever and night sweats, B symptoms, a PET scan showing lymphadenopathy above and below the diaphragm with FDG uptake in bony lesions, and a lymph node biopsy confirming relapsed Hodgkin lymphoma. So, given the following options, what would be the best next step? BV combined with nivolumab without an autologous stem cell transplant, pembrolizumab combined with GVD followed by autologous stem cell transplant, BV with bendamustine followed by autologous stem cell transplant, ICE chemotherapy followed by radiation, or just BV alone.

And here, you know, the clear option is pembro-GVD followed by autologous stem cell transplant. Not keen to use a BV-based regimen in a patient who received BV in the frontline and now has relapsed. And importantly, this patient should certainly be planned for autologous stem cell transplant. And so, we've seen that PD-1 blockade really leads to the best outcomes in patients in this situation.

Finally, we'll discuss managing adverse events of immunotherapy. So, immune-related adverse events tend to occur early, within weeks or months of initiation of checkpoint blockade, and most immune-related adverse events are low grade. And this slide demonstrates all the different organ systems where you can have immune-related toxicity. This slide here shows the time to onset of immune-related adverse events after PD-1 blockade. Skin toxicity tends to show up the earliest. You know, sometimes renal toxicity is a little later, but usually all of these adverse effects are within, you know, the first month to 3 months of treatment.

Nivolumab-AVD was pretty well tolerated. The rate of immune-related adverse events was relatively low. This slide here is showing kind of ALT and AST increase, but these were not immune-related adverse events. For the most part, the rates of significant immune-related

toxicity was quite low.

When you combine brentuximab and nivolumab, about 14% of patients require systemic corticosteroids for immune-related adverse events, and the types of things you might see include pneumonitis, rash, colitis. These are the typical immune-related adverse events that we see with checkpoint blockade. Now, if a patient has a mild grade 1 immune-related adverse event, you can continue the PD-1 blockade, and for example, skin manifestations can be treated with a topical steroid cream.

For patients with more notable immune-related adverse events, you do typically want to interrupt therapy and treat with steroids. And importantly, you want to taper those steroids slowly over no less than a month. I think we see this all the time when patients get a shorter course of steroids, and then those steroids are tapered off quickly. The immune-related adverse events can recur. So important to taper the steroids slowly.

Another important callout: You can treat through endocrinopathy, so thyroiditis. You can continue the checkpoint blockade; just replace the hormones.

So, some common questions that arise: Do immunosuppressive agents impact the efficacy of immunotherapy? It's not clear evidence that that's true in the primarily solid tumor experience. Are immune-related adverse events associated with efficacy? Right? So, if I get an immune-related adverse event, am I going to respond better? There's some conflicting evidence about that. Are there effective biomarkers to predict the development of immune-related adverse events? That is an active area of ongoing research. And is it safe to rechallenge patients with PD-1 blockade after resolution of an immune-related adverse event? Now, that depends on the severity. Often, immune-related adverse events are likely to recur, and I think sometimes we can consider using concurrent low-dose immunosuppression. You know, but overall, especially if a patient had a significant immune-related adverse event that's grade 3 or higher, I typically don't rechallenge them.

So now to conclude, we talked about early-stage Hodgkin lymphoma. We talked about unfavorable and favorable disease and the risk factors that lead to those designations. With favorable early-stage Hodgkin lymphoma, we can use combined-modality therapy or PET-adapted chemotherapy alone. But usually, these are shorter courses of chemo. For unfavorable early-stage Hodgkin lymphoma, again, combined-modality therapy, although now with more cycles of chemo, higher doses of radiation, or PET-adapted chemotherapy alone with the omission of radiotherapy. However, typically you want to use a full course of six cycles of systemic therapy, and you can now use the novel agents brentuximab vedotin and nivolumab if a patient has unfavorable early-stage disease.

For advanced-stage Hodgkin lymphoma, now, you know, the standards are either nivolumab-AVD for a full course of six cycles or BrECADD, PET-adapted BrECADD, and that can be as short as four cycles if a patient has a negative PET scan after two cycles of BrECADD. BV-AVD and ABVD remain options in certain circumstances, but that's really if for some reason you don't have access to, or a patient is ineligible to receive nivolumab, that's when you might want to consider those options.

For relapsed/refractory Hodgkin lymphoma, the standard remains salvage treatment followed by autologous stem cell transplant in patients who are sensitive to therapy, and we have tended to incorporate the novel agents into the salvage treatment of relapsed refractory Hodgkin lymphoma.

Finally, in later lines of therapy, we can use, you know, BV or PD-1 blockade, especially if patients have not received those agents.

Just wanted to conclude by thanking you for your attention to today's program.

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