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EPISODE 4 V2 BREAK APART

MTT NHL & HL

Loretta Nastoupil, MD: Welcome to this *Med Table Talk*™ series on Lymphoma: The power of the community translating innovations into care in non-Hodgkin and Hodgkin lymphoma.

This is the final part entitled, "Checkpoint Conversations: Integrating Immune Checkpoint Inhibitors in Hodgkin Lymphoma." My name is Dr. Loretta Nastoupil from the University of Texas, MD Anderson Cancer Center. Welcome back to my fellow colleagues. Would you please quickly introduce yourselves.

Ann LaCasce, MD: Thank you. My name is Dr. Ann LaCasce from Dana-Farber Cancer Institute in Boston.

Amitkumar Mehta, MD: Hi, I'm Amitkumar Mehta. I am at the University of Alabama at Birmingham.

Dr. Nastoupil: Let's get started. I'd like to hand this over to my esteemed colleague, Ann LaCasce, who's a world expert on Hodgkin lymphoma. Ann.

Dr. LaCasce: Thank you so much. I, you know, I really love treating this disease because the outcomes for most of our patients are really very, very favorable. And I think a lot of

what we're doing now is trying to figure out how to deescalate therapy in patients who don't need a therapy such as radiation, particularly in the early stage setting.

So, this is a reminder of the staging for Hodgkin lymphoma, and we use the Lugano Staging. Hodgkin is a relatively uncommon disease. There are fewer than 9,000 cases in the US, so I think we have to, per year. We have to keep in mind that this is often a disease that our community partners may not manage very frequently; and there are some nuances in trying to sort through the recommendations, which are very, you know, I think more than any disease in lymphoma, there's a lot of room here for personalizing the therapy to the patient, both based on age and comorbidities and risk of late, late toxicities.

You can see here the International Prognostic Score, which also looks at some variables, both clinical and laboratory based, that can help us predict outcome in patients with advanced stage Hodgkin lymphoma there. I'll also mention there is what's called the HoLISTIC calculator. There's a new multi-s, multi-national calculator that you can get online that may refine this even a little further with more modern therapies.

And then when we think about early stage patients, we group it, group these patients according to how many risk factors they have, which look at things like bulky mediastinal disease; B

symptoms, which are prognostic in early stage Hodgkin lymphoma; and number of sites of nodal involvement.

So, these are the NCCN Guidelines for relapse and refractory Hodgkin lymphoma. As I mentioned, you know, most of our patients are going to do extremely well with frontline therapy, but we do still have patients who have primary refractory or relapsed disease. It's probably dropping now that we are incorporating novel agents in the upfront therapy, so probably on the order of 25% of advanced stage and maybe 10 to 15% of early stage patients will have relapsed or refractory disease.

And I think, you know, the NCCN Guidelines are really helpful for putting, again, a framework around what the therapeutic options are; but we really need to think about the individual patients when we select a next line of therapy because, as you can see here, there are many, many potential options.

So, what has come on the scene now, now probably seven or eight years ago, we had the approval of pembrolizumab and nivolumab in Hodgkin lymphoma. Hodgkin is uniquely sensitive to checkpoint inhibitors because of the biology of the disease. There is upregulation of 9p24, the chromosomal home of PD-L1 and PD-L2. So the response rates in Hodgkin lymphoma exceed really any other oncologic disease out there.

So, these are very important therapies; and what we have seen with the introduction of checkpoint inhibitors in Hodgkin, particularly initially in the relapsed and refractory setting, is that our outcomes are dramatically better. So, for patients who are going to stem cell transplant, autologous stem cell transplant, I think, remains the standard of care for patients with relapsed or refractory disease. But you've got to get them there first, and using checkpoint inhibitor in that setting in second-line therapy for those who have not received it frontline, which is going to start to happen soon given some recent data, I think is very, very important.

So, maybe I'll pause there and ask for comments from Amit and Loretta.

Dr. Mehta: No, I think, you know, the Hodgkin's treatment has revolutionized so much; and I think the main factor is addition of brentuximab vedotin as well as the checkpoint inhibitor or the combination with chemotherapy. And the prime focus, as you mention, Ann, is to avoid long-term toxicities.

Most of these patients are very young, and we learned so-called our mistakes in the past, you know, that we treated this patient extensive with chemotherapy, intense radiation. We learned quickly that these patients are coming with secondary cancers or heart conditions. That's why we need to modify the approach.

But those, the brentuximab vedotin, as well as checkpoint inhibitor has changed the treatment paradigm, quite a bit of Hodgkin's. It's very exciting time as you mentioned that less and less patients are getting relapsed disease; and for them also, we have novel, novel approaches. So, very exciting time for Hodgkin's.

Dr. Nastoupil: Yeah, I think one thing that's really intriguing about Hodgkin lymphomas, we can learn a lot about drug development. So, if you think about just ten years ago, it was almost daunting to even consider a career as a clinical investigator in Hodgkins lymphoma because the outcomes were so good with standard chemotherapy. Why would we even go there?

But we learned a lot about the biology of the disease, and that did inform the next wave of clinical trials. So, we didn't stop because we weren't curing everybody; and even though we were doing a really good job for the majority of people, there was still room for improvement.

And now we're even starting to question sort of these paradigms of do you have to have chemotherapy, even in a disease where the cure rates are so high with standard chemotherapy. I think this is an important lesson for all our lymphomas and even solid tumors. If you can really understand the underlying biology of the disease, it does open the door for you to really question

some of these things that we found were held to be so important and so true and still, again, lead to improvements. I mean we're seeing improvements in randomized, Phase III trials in frontline Hodgkin lymphoma now with some of these novel therapies, which is really exciting.

Dr. LaCasce: Yeah, I totally agree; and I think it's been an amazing evolution over time, and we've seen brentuximab plus AVD compared to nivolumab plus AVD. This was a large national study including pediatric and adult patients and Canadian patients, and it accrued ahead of schedule. This was a cooperative group study that was really in a very rare disease. This is only advanced stage Hodgkin lymphoma. And I think it's really a model for collaboration, and a lot of community sites were able to open this study.

So, I think it, it really serves as a roadmap for how we can work together; and now there is another study that's just open in early stage patients asking if we incorporate brentuximab and nivolumab for those patients, can we reduce the use, use of radiotherapy; and can we improve outcomes? But it takes large numbers of patients because our outcomes are so good already. When we're looking for a small difference, you really have to enroll a lot of patients. So, it's been a really exciting time, I think, in, in clinical trials and drug development.

These were the original studies looking at nivolumab. These were patients who had been very heavily pretreated; and at this point, you know, this was eight or nine years ago, we really had very few options for patients who had relapsed after autologous stem cell transplant. And these, these agents came along; and we were seeing, you know, 75% of patients, 60 to 75% of patients were responding.

Although, the number of patients who had complete remissions was relatively low, many patients could have very good quality of life with partial remission over months to years. And I've seen this. You know, patients relapse post-auto. I've a patient who was on a checkpoint inhibitor for seven or eight years before we needed to consider our next option. So, it's really been quite interesting.

I'll ask Amit, Loretta, anything to add?

Dr. Mehta: No, I think you, you brought up a good point, Ann. And, you know, I've also seen in my, my clinical practice essentially the checkpoint inhibitors, when I discussed with my patient, I highlighted that this, Hodgkin's is now more like a chronic disease, right? I mean they come and they get their infusions. Their quality of life, as you mentioned, is great. I, you know, they, they work full time with minimal side

effects. Even though you do a PET scan, you see a disease; but, you know, they are in that disease control mode for years.

So that has, you know, completely changed the perception that we used to see for Hodgkin's is either chemo and radiation. We don't want to see the disease on the scan. Compared to here we are, they're okay with single disease as long as they're living almost normal life.

Dr. Nastoupil: Yeah, I agree with that. I think maybe the only thing I may add or challenge is for those few patients who have a complete response, do we really need to keep them on continuous therapy?

So, I've had two patients in my practice that were treated on protocol that there was some wiggle room there that if they'd been a CR for X amount of time, they've been on drug X an amount of time, we could stop them. And I do have two that have been off therapy now for years, and so, again, those are very minority of situations; and I completely agree with Amit, those that are in a PR and they've got fantastic quality of life, and they're just coming to see us every couple of weeks, that's a tremendous improvement. I think there are questions about those that have a complete response, albeit a small population. Can you just stop that therapy, and when is the optimal time to stop it?

Dr. LaCasce: Could, now I think that's a very good point.

And the tolerability of PD-1 inhibitors in this disease, you know, fortunately, it's about 5% of patients who have to come off therapy for immune-related adverse events. And I think it was really interesting in the S1826, the study comparing BV-AVD to nivo-AVD. Twice as many patients discontinued brentuximab as nivolumab in that study, and the toxicity profile was very much in favor of the patients receiving the PD-1 inhibitor.

And I think the other population, you know, we think of this as a disease of young adults. The median age is, you know, 39; and most of the patients are in their 20s and 30s. But we also have these elderly patients with, you know, as their immune system, they get immune senescence; and they can get these EBV-driven Hodgkin lymphoma, and our standard therapy is BV-AVD is just not tolerable. You either have to do it sequentially.

But in the, in the S1826 study, we saw really remarkable responses in nivo-AVD, and patients tolerated it well. So, I think we're about to really see a shift in how we treat our older patients. And it's, it's really gratifying to be able to offer something to someone who's in their 70s and 80s and have them tolerate it and actually go into complete remission.

Let's see, so these are the curved pembrolizumab. You know, I think most of us think that the two approved agents have very similar efficacy and toxicity; and, you know, it, we use them sort of interchangeably, depending upon the setting.

All right, so we've talked a lot about CAR T-cell therapy in non-Hodgkin lymphoma, both in aggressive and follicular and mantle cell. And there have been some studies in Hodgkin lymphoma, and thus far I think the responses and durability of responses have been somewhat disappointing; and I, and I'd love to hear colleagues' thoughts.

I wonder whether, you know, there are very few tumor cells, the Reed-Sternberg cells where the minority of cells and they, they're surrounded by this tumor micro-, microenvironment that I think is somehow interfering with the effect of CAR T. But I would love, love Loretta and Amit, to sort of hear your thoughts on is this a strategy that's going to be successful in Hodgkin lymphoma?

Dr. Nastoupil: And Ann, I think, Ann you've hit the key point, at least based out of our current understanding. It's probably the microenvironment that's triggering these sort of short responses and hindering the progress to be made. And there have been strategies trying to examine different lymphocyte-depleting

regimens, including the incorporation of bendamustine to try and address that.

You know, other additional strategies may be including adding in checkpoint inhibition. But as of right now, we definitely don't see the efficacy in Hodgkin lymphoma that we've seen in other B-cell malignancies, even though we have a target. CD30 is clearly an effective target if you think about the efficacy of brentuximab vedotin, but I do think it's probably that negative microenvironment that's hindering either the trafficking of those T-cells or the function once they get there. Amit, what are, what are your thoughts?

Dr. Mehta: Well, I think I totally agree, and I think, you know, so far the CAR T success, the maximum success that we have seen is myeloma and lymphoma. And solid tumors and probably the same reason. A very inhibitory tumor microenvironment is not allowing the T-cells to kind of, you know, have an anti-tumor activity.

So Hodgkin's is a classic example with very few tumor cells. And, you know, I think truly the PD-1 success story and the, the results are so stellar that there are very, very few patients who could actually make it to the, the clinical trials for CAR T. But I totally agree that CAR T is not as, as good as in other B-cell lymphomas in Hodgkin's.

Dr. Nastoupil: So I guess the question, do you think that applies to bispecifics as well?

Dr. LaCasce: That is a great question. And this, there are trials that have just started looking at CD30, CD3 bispecifics. And one, one hopes maybe with repeated administration, maybe that will help overcome some of the resistance that this disease seems to have to CAR T. But I also worry about the same issues, whether they'll really penetrate into the, to, to the tumor microenvironment; and what are the T-cells that we're going to rely upon to cause the destruction of these Reed-Sternberg cells? What is their function and their fitness? May be an issue.

Dr. Mehta: Yeah, that's true. I, I, you know, I don't know whether the, the bispecific engaging CD3 has, you know, good responses in Hodgkin's. But the other bispecific, which is engaging the NK cells, you know, in combination with PD-1 has shown responses in terms of more complete responses. But I mean, you know, it's also being explored in other combinations. But, you know, so far nothing has caught my eyes that this could be a, you know, the next level treatment for Hodgkin's.

Dr. LaCasce: Yeah, those NK, you know, I think there are a number of other PD-1 with TIM-3 or other, you know, bispecifics that are being studied or using NK cells, donor NK cells, and we

see these responses, what with the NK cell infusions with the bispecific to CD16 and CD30. But again, they're not durable; and I think we have a ways to go for that very small population of patients.

But I think, you know, because patients live so long with relapsed and refractory Hodgkin lymphoma, I think we all are accumulating some of these patients in our clinics. And, you know, I think allogeneic stem cell transplant is still something that we are referring patients for; and there's a lot of resistance on the part of the patients because they, you know, they've done well for so long, and the restrictions and the risk associated with transplant seems to be an issue.

So, moving on to talk about disparities among patients with Hodgkin lymphoma, you know, we've seen in, in multiple studies that patients who are African American or Hispanic populations appear to have inferior outcomes. And whether that is related to being able to access the same degree of care and the same therapies that our other patients are receiving, I think that's probably a major driver.

I think we don't know of biology-specific reasons at this point, but it is certainly, there's been some data, particularly in pediatrics, where they've seen that patients, you know, may do well initially; and they're treated on clinical trials. I think

the pediatricians do a very good job of enrolling the majority of their patients in the context of clinical trials. But then when those patients relapse, they don't necessarily have access to trials, and that's where those disparities really have been magnified. Thoughts on that, Amit?

Dr. Mehta: Well, the patient age group is also different. We have, you know, younger age group as well as older age group; and perception of clinical trial is different based on even, you know, ethnicity and, and the cultural background.

So, that has been a, been a challenge; and I think as you mentioned, I commend the S1826 trial that they could enroll so many patients. And the trial enrolled very quickly, and that required, you know, both, both, both the patient popula-, older as well as younger.

And historically, the older population has not been enrolled that much in the clinical trial either. So, I think that age group has a significant role in Hodgkin's clinical trial enrollment.

Dr. Nastoupil: And I think the other thing to consider is that, again, these patients might have unique sort of barriers that we don't typically see in our 63-year-old B-cell lymphoma patients. And that, oftentimes, they're trying to have a life or they're

trying to complete school or they're trying to pre-, you know, be caregiver for a number of patients. And so I think retention is another key aspect. Not only can we get them on these studies, but can we continue to follow them long term so that we know what the impact is on quality of life and sort of their transition from being a young adult to a fully functioning adult? I think there are unique questions in this population that we need to do a better job studying.

Dr. LaCasce: I think that is really a very important point, and I think in our underrepresented populations, there may be more psychosocial barriers. Some of these folks may be taking care of siblings or, you know, you add that on top of all the other barriers that already exist; and it is, I agree, this is a patient population that has a lot of need and suffers a lot from a psychosocial perspective and from the late effects.

Dr. Nastoupil: Well, I appreciate, Ann, you've done a very nice job of walking us through the data in Hodkin lymphoma; and now we'll spend a little bit of time just sharing our insights. Checkpoint inhibitors are clearly an effective strategy in Hodgkin lymphoma, but we see the CAR T and bispecifics falling slightly short, probably due to the biology that seems to be unique to this entity.

And so, Amit, what are your thoughts about kind of where we go next in terms of engaging our community providers but also sort of next steps in terms of clinical research?

Dr. Mehta: So what, you know, I think you, you brought up a good point about the, the development of newer therapies in Hodgkin's. Ann also mentioned that this is a relatively rare cancer.

So, what I've seen is in community, as people don't see this on a regular basis, they may not be up to date with what is going on. And I've seen still, you know, ABVD-based regimen or ABVDs being used. So, I think that education piece is very, very important.

And, you know, we started with ABVD. Suddenly we were r_____ approach in advance. And then we had ABVD which was getting better, and the community was, you know, treating more patients; and suddenly we had a change in the treatment in a frontline setting. So, there's a lot of movement in a rare disorder where people are not routinely seeing this, so I think education and communication to the community doctor is the key factor here.

Dr. Nastoupil: Ann?

Dr. LaCasce: Yeah, no, I really agree. I think there are, you know, with Hodgkin lymphoma, you have to treat on time. You

don't delay. You don't need growth factors if you're using BV-AVD, and it's very- You know, there you have to use growth factors, and patients have a lot, a lot of symptoms if you use the pegylated form.

So, I think we've really, because it is a rare disease, just as you suggested, we need to really focus on supporting our community physicians when they see these patients. And really when they relapse, we really need to see those patients to get them to stem cell transplant using PD-1 inhibitors as salvage in most patients because the outcomes are really very, very favorable. And, you know, these are patients who then go on to have, you know, long, long life expectancy. But we need to get them there.

So again, I think it's about education, it's about community, and it's about working in teams.

Dr. Nastoupil: And in a perfect world, what would you hope to see?

Dr. LaCasce: So, I think in a, in a perfect world, we'd love to have patients being referred in for consults or shared care so that we can really make sure that we personalize the therapy to the individual patient thinking about age and risk of comorbidi-

, you know, with comorbidities and risk of late effects, particularly with early stage disease.

So, it really takes a group effort; and you need to engage fertility specialists in some situations. Most of our therapies don't cause infertility, but it's some- Now, these are things that we don't necessarily talk a lot about with our 65-year-olds, you know, diffuse large B-cell lymphoma patients. So it really, the psychosocial issues, the, you know, the pulling people out of their, this critical time in their lives when they're really, you know, trying to establish themselves. I think we can't underestimate that, so I think it's, you know, again, it's been a theme over and over again. But, you know, working together in good communication all around.

Dr. Nastoupil: Amit?

Dr. Mehta: I totally agree. And as I, I, I tell my fellows, there are few cancers who can be completely cured; and you want to master them. You don't want to make mistake in that. This is one of them, right? That if you do it right, you know, this, this will be cure. And, you know, minimal use of radiation. We're very select; that is also important as people will live longer, and you don't want to expose them to long-term toxicity, team approach. And younger patients, they have different needs,

different, you know, requirements. So, we have to align with that.

And for the community doctors, I always say that this is a rare cancer. It's always better to pick up the phone and call your colleague at the academic centers who are doing on a regular basis. At least get an idea what is going on so that you can, you can do it right.

Dr. Nastoupil: Absolutely great. And I think the only thing I can add to that is that I hope we can learn in other lymphoma subtypes how to conduct effective Phase III studies in rare tumor types. So, kudos to Ann and your colleagues.

Dr. Mehta: Missed that one.

Dr. Nastoupil: Thank you for joining us for this *Med Table Talk*™ on Non-Hodgkin and Hodgkin lymphomas, Drs. LaCasce and Mehta, and thank you for joining this discussion today.

If you missed parts 1, 2, or 3, make sure you go back and join us for an exciting discussion. For additional resources, please see the activity website. When you claim credit, please complete the post-assessment questions and evaluation. Take care.

END OF EPISODE 4