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Myeloma Matters: Bispecific Antibody Horizons: Dosing Strategies and Meeting Updates in Myeloma Care

Announcer:
Welcome to ReachMD. This activity, *Myeloma Matters: Bispecific Antibody Horizons, Dosing Strategies, and Meeting Updates in Myeloma Care,* is jointly provided by RedMedEd and the Multiple Myeloma Research Foundation. Prior to beginning the activity, please be sure to review the faculty and commercial support statement as well as the learning objectives.

Welcome to the *Myeloma Matters* podcast hosted by the Multiple Myeloma Research Foundation and focusing on topics related to improving outcomes for myeloma patients. This podcast is based on a roundtable discussion with Dr. Saad Usmani, Chief of Myeloma Service at Memorial Sloan Kettering Cancer Center; Dr. Joshua Richter, Associate Professor of Medicine at Tisch Cancer Center Icahn School of Medicine at Mt. Sinai; and Ashley Steinberger, a nurse practitioner at Memorial Sloan Kettering Cancer Center.

This episode of *Myeloma Matters* reviews the latest data on bispecific antibody therapy for relapsed/refractory multiple myeloma, as discussed at the 2024 American Society of Clinical Oncology and European Hematology Association annual meetings, including information about the use of fixed-duration dosing to mitigate adverse events.

Dr. Usmani:
Hello, I'm Dr. Saad Usmani, Chief of the Myeloma Service at Memorial Sloan Kettering Cancer Center. Welcome to this episode of *Myeloma Matters*. Joining us today are my colleagues, Dr. Joshua Richter and Ashley Steinberger. I invite them to introduce themselves, starting with Dr. Richter.

Dr. Richter:
Thank you so much for having me here today. My name is Josh Richter. I'm an Associate Professor of Medicine at the Tisch Cancer Institute Icahn School of Medicine at Mt. Sinai and Director of Myeloma at the Blavatnik Family Chelsea Medical Center at Mt. Sinai. I'm excited to be talking about myeloma today.

Ms. Steinberger:
Hi, my name is Ashley Steinberger. I am a nurse practitioner at Memorial Sloan Kettering Cancer Center in New York City.

Dr. Usmani:
Wonderful. Thank you, Josh and Ashley, for joining. We'll start our discussion with a couple of abstracts that were featured recently on teclistamab. We'll start with the MajesTEC-1 updates specifically, focusing on the prophylactic use of tocilizumab and the incidence of cytokine release syndrome (CRS).

If you recall, MajesTEC-1 was the pivotal trial that led to FDA approval of teclistamab back in the fall of 2022. The original cohort of patients was a total of 165 that had not received prophylactic dosing. Subsequently, there was a cohort of 24 patients that went on to receive prophylactic tocilizumab. This particular abstract that was presented at ASCO highlighted the reduction in overall CRS with prophylactic dosing, which went from 72% down to 25%. Grade 1 CRS, which was around 50% in the original trial, went down to 8.3 in this tocilizumab prophylactic cohort. However, the grade 2 percentage was about the same, 16.7%. There were no disease characteristic differences between the groups, but I found this data quite intriguing.

They also presented on the responses in the two cohorts, and the response appears to be comparable compared to the overall original patient population of 72 versus 63%. If you look at the follow-up time period between the cohorts, it was a little different, so you do see some differences in the quality or depth of response. The median follow-up was only 8 months or so. On the original cohort, the median

follow-up is reaching close to 3 years now.

What are your thoughts about these findings? We can start with Josh, and then I'll go to Ashley.

Dr. Richter:
One thing to note is that the three of us work in institutions where we treat dozens and dozens and dozens of myeloma patients per day, and we have whole teams set up to deal with things like cytokine release. One of the things that makes me very excited about this data is, I think, by bringing down the overall rates of CRS, there's a better chance of getting it in the hands of some of our community colleagues. To me that's the biggest thing: a better pathway to outpatient dosing and community dosing.

Ms. Steinberger:
I definitely agree. I think it's going to bring down some of the barriers in starting the step-up dosing. Some patients are hesitant because of the admission to the hospital, so if we can somehow mitigate the CRS and make it safer for patients to get it as outpatient, then more patients would be willing to proceed with the drug. I also think it's better for the hospitals, as well, to not burden the floors with more admissions.

Dr. Usmani:
Have you started to use teclistamab in the outpatient setting yet? Or, if you're doing it, how are you picking patients for that?

Josh, how are you guys thinking about this at Sinai?

Dr. Richter:
We haven't quite delved into the full outpatient dosing just yet, because I think a lot of patients that we tend to give commercial teclistamab may be a little bit higher burden, so a little bit higher risk overall. We have what I like to call the early-release program, which is we admit you to the hospital and almost everyone will get CRS within the first one or two step-up doses. Within 24 hours of that, we'll actually send them home, because our internal data shows that the likelihood of severe CRS recurring afterwards is extremely low. In fact, most people don't get any, given the long half-life, and a handful get only grade 1 CRS, so we send them home with some steroids, just in case.

Dr. Usmani:
Ashley, what are your thoughts?

Ms. Steinberger:
We have done a few as outpatient, actually, where they'll get the dose outpatient and then they go home with a vital-signs monitoring machine that we can use to closely monitor their vitals and be notified if any of the vitals are abnormal. So, it makes it safer for them but, like Josh said, they have to fit a strict criteria and have a low burden of disease. The people that go on this drug typically have a higher burden, so most of them are getting admitted, but some of them do fit the criteria to safely have it as outpatients.

Dr. Usmani:
I know that some of the Sinai colleagues have done this for CAR T-cell therapies, as well, and we are doing the same for both bispecifics and CAR T.

The other important abstract was presented at EHA from our colleague at Memorial Sloan Kettering (MSK), Carlyn Tan. This was the MSK experience of less-frequent dosing.

One of the concerns that has been raised regarding BCMA-directed bispecifics is patients getting increased risk of infections—bacterial, viral, and even opportunistic infections—with ongoing treatment with teclistamab and other BCMA-directed bispecifics requiring intravenous immunoglobulin (IVIg) support for hypogammaglobulinemia, etc.

In this cohort, 86 patients got at least one dose of teclistamab with the median of six prior lines of treatment. One third of the patients had received a previous bispecific-directed therapy, as well. There were a couple different groups of patients; the early initiators were the patients that were treated in the first 4 months and, Josh, Ashley, you guys know how desperate we were for other options at that time. We all had long wait lists for CAR T cells, and we just let teclistamab loose on that patient population. Then we had subsequent patients where we had more experience with teclistamab, and we started to switch patients from every week to every-2-week or every-4-week dosing. What Carlyn Tan demonstrated is that, even after that switch, that tended to happen around the 3-month mark with subsequent follow-up of 6 months, more than 90% of the patients actually maintained their initial responses.

Our group had initially decided that, because the median time to best response is within about three cycles or so in patients who are already demonstrating responses of VGPR or better, let's start dialing down the frequency of treatment. And in our experience it appears that patients continue to maintain responses. I know that Carlyn will also be updating the infection data, but I thought the fact

that more than 90% of the patients actually have sustained responses was pretty neat after that switch.

So, Josh, what are your thoughts around this data? How has the Sinai experience been with the less-frequent dosing? Is it any different?

Dr. Richter:
One of the things that this data brings up is that we have to stop thinking about all of these drugs like we did classical chemotherapy. It's not all about dose intensity. It's not all about dosing higher, dosing lower. It's about getting your immune system to do what you need it to do and trying to find that Goldilocks zone between forcing every T cell to wake up and fight cancer and then taking every T cell away from fighting infection. So, I think your description of the landscape is perfect.

When these first came out, we were desperate to get these drugs into the hands of our patients. Now we have taken a very similar path, just as you guys have, which is quickly getting to less-frequent doses. I think a lot of us try to follow the daratumumab-like scheduled 2 months of weekly, 4 months or every other week, and then monthly. But there are patients that are in complete response (CR) or better within a few cycles. For some of those, we feel absolutely fine going right, pretty quickly, to monthly dosing.

Dr. Usmani:
Ashley, what are your thoughts? Because you actually take care of a lot of these patients.

Ms. Steinberger:
I have similar experiences. Definitely, patients are tolerating the drugs better when they are given a little bit less frequently, and they are getting less sick and the immunoglobulins come up a little bit better. It just seems like they continue with a good response. We have a patient that sometimes will travel for 3 months and come back and still have undetectable disease, so it seems to be that they get, some of them, very deep durable responses.

Dr. Usmani:
Just staying on that theme, with these amazing results with BCMA-bispecifics in the relapsed state, it was only a matter of time that we started to think about combining them with other therapies in earlier lines of treatment and we actually got the first glimpse of the MajesTEC-7 safety cohort.

Josh, I would love your comments on this frontline treatment regimen. What was the regimen and what were the data?

Dr. Richter:
It's been an exciting 6 months or so. We've seen many years of everyone focusing on the relapsed space, and then within the last 6 months between seeing transplant-eligible studies like Isa-KRd, transplant ineligible like Isa-VRd, and now with MajesTEC-7 giving teclistamab, Darzalex, and lenalidomide, I think we've really seen this push to get these unbelievably deep responses up front. Maybe so deep that we don't even need to get to the relapsed setting.

MajesTEC-7 was a multi-arm study. What they really put forward data-wise was the teclistamab, Darzalex, lenalidomide cohort, and median follow-up now of almost 14 months. And the data's not unexpected.

From a safety standpoint, about two thirds of patients are going to have CRS. Most of this occurs in cycle 1. Immune effector cell-associated neurotoxicity syndrome (ICANS) is very rare. I think they had only one case that was grade 1. Most of these patients are able to maintain good dose intensity. Really, the big side effects, besides heme toxicity and lowered blood counts, are infections. We saw a fair amount of infectious complications. This was not unexpected when you start to mix CD38 and BCMA. And, I think, what Ashley alluded to before was perfect, is that with BCMA therapies we have to be concerned about hypogammaglobulinemia and the infection. And when you mix Darzalex in, it can make it a little more profound.

But, you know, I think one of the things that we really liked was the efficacy of this regimen. The overall response rate was 92.3%, with more than 92% of patients having a very good partial response (VGPR) or better. So a highly effective regimen. So far, no one has progressed. So I think T-cell redirection with the recent approval on first relapse established the dominance there, and now we're starting to see some great data in frontline.

Dr. Usmani:
Ashley, what do you think about the data? Oh! One thing I want to highlight with this regimen, I think the teclistamab dosing follows that of daratumumab. I think you go from weekly to every other week to monthly dosing. That's the piece that I also liked about how this cohort was run and designed, because that will help mitigate that infection risk issue.

Ashley, what do you think?

Ms. Steinberger:

This is really interesting, and it could change a lot of what we do as up-front treatments for multiple myeloma if the response rate is this high. We're learning more about how to combat infections and prevent them.

Dr. Usmani:
MajesTEC-7 is a multi-cohort phase 1 study conducted to figure out safety, and then there's a randomized trial. This regimen is being developed for transplant-ineligible or older patients. It's going to challenge MAIA, so daratumumab, lenalidomide, and dexamethasone (DRd). I'm really looking forward to the phase 3 portion of this trial opening and for us all to enroll patients on it, because the depth of response we're seeing is amazing. And the fact that MAIA has already made such a big impact for that older myeloma patient population, seeing a regimen that can even supersede that... I'm really looking forward to that. I'll be curious to see how this plays out and what that final clinical trial design looks like.

Let's turn our attention to data on other BCMA-directed bispecifics. Dr. Mohty presented updated efficacy and safety results from the MagnetisMM-3 trial that has now had more than 2 years of follow-up after the last patient was originally dosed. This is long-term survivorship from that original clinical trial. A total of 123 BCMA treatment–naïve patients with relapsed or refractory disease were treated with elranatamab. A third of those patients had extramedullary disease, and 15% had high-risk karyotypic abnormalities. The median prior lines of treatment was five. The vast majority of patients—almost 97% of this population—were triple-class refractory. The overall response rate was very similar to what had been reported with teclistamab, at around 61%. Minimal residual disease (MRD) negativity was 90.3% in the evaluable patients who had CR or better, which was around 38% or 39% if I remember correctly. The median progression-free survival (PFS) was quite impressive at 17.2 months, and median OS for this population was over 2 years. For context for this triple-class refractory patient population, the median OS we would expect is only 8 to 9 months. So amazing results, and I don't think they reported any new safety signals from an infection risk or long-term follow-up perspective.

Josh, what are your thoughts about the elranatamab long-term follow-up?

Dr. Richter:
I think this confirms the data we've seen all along, with some great data presented by Dr. Lesokihn at your center. It's nice to see the follow-up. It's really nice to see no increase in second primary malignancies, because we've seen that, unfortunately, with the Carvykti product. Head-to-head between this and teclistamab, it's hard to say a lot, though the nice features are that it's a shorter step-up dose and fixed dosing as opposed to weight-based. But, again, another great asset to have in our toolbelt.

Dr. Usmani:
Ashley, what do you think? We've had experience at our site with elranatamab doing the clinical trial phase and now with the commercial product.

Ms. Steinberger:
I think that this is, again, what Josh said: it just confirms that people do get deep and durable responses to these bispecifics. And this is in BCMA-naïve patients, so I would be interested to learn more about the patients that have had BCMA and had elranatamab and if they did respond, because, with teclistamab, I think that you still could respond even if you had prior BCMA.

Dr. Usmani:
I'm going to now turn to Josh to review data on BCMA-directed bispecifics.

Dr. Richter:
Let's take a look at what's on the horizon for treatment for relapsed and refractory myeloma.

Saad, as you pointed out, we already have two FDA-approved BCMA-targeting bispecifics: teclistamab and elranatamab. But there's some good data coming down the pike on a couple others, including linvoseltamab and ABBV-383. And we recently saw some data presented by Dr. Lentzsch over at Columbia from some of the updated phase 1/2 results of the LINKER-MM1 study.

At a median follow-up of around 14.3 months, we saw very high efficacy. In myeloma you're never supposed to compare trial-to-trial, so you have to say that statement, then you take a deep sigh, and you go on to compare trial to trial. We see an overall response rate of 71%, which is, so far, the highest in class. But, again, there are noticeable differences between the different trials, so it is a quite high number, with the others, at around 63% to 64%, in the same ballpark. You saw a CR rate of 50%, median duration of response was almost 30 months, PFS not yet reached, 70% of patients were still in remission at the 12-month mark, and median OS was 31 months. So, a very efficacious drug.

In terms of the safety profile—again, like with all the bispecifics—the big treatment adverse events are things like CRS and ICANS. Overall, the CRS rates were relatively low. The majority were grade 1 and grade 2. In terms of efficacy and safety, teclistamab, elranatamab, and linvoseltamab are all very similar. Maybe one drug is slightly higher in the perimeter, one is slightly low in that

parameter, but I think the three are all great drugs. We're really waiting for the LINKER-MM3 study comparing against elotuzumab/pomalidomide as a registration phase 3 for future data.

The next drug we're going to discuss is the bispecific antibody ABBV-383. This was presented by Dr. Isoken and was another large trial: 220 BCMA-naïve patients with a median five lines of prior therapy. And, as Ashley pointed out, we know this great data in a BCMA-naïve population. We really need more data about evaluating these drugs in patients who have had other BCMA assets like CAR T therapy.

One of the really nice things about ABBV-383 is that it goes right away to a monthly dosing. A really great quality-of-life thing for patients, because the other drugs will stay weekly and/or go to every other week. We do have data for extending out teclistamab and elranatamab to monthly. Linvoseltamab actually has built-in, when you get to week 24, if you are in a VGPR or better you go to monthly dosing, but here with ABBV-383 you go right away to monthly dosing well within perimeters.

In terms of CRS, overall very well in line with some of the previous assets. When we looked at the 40-mg and 60-mg doses given every 3 weeks, we saw CRS rates of 71% and 70%, respectively, but at the every-4-week dosing it goes all the way to 43%, so really well tolerated overall. When we talk about the overall response rate, looking at the different dosing strategies, this is very much in line with the other bispecifics. With the 60-mg every-4-week dosing, we see an overall response rate of 65% with more than half of the patients achieving a VGPR or better. A little bit of a shorter follow-up with this cohort, but overall responding very quickly, median time to first response of around a month. Overall, I think we can find little perimeters here and there that may be subtly different between the different BCMA assets, but they're all pretty much in line safety- and efficacy-wise.

Dr. Usmani:
The key takeaways from the BCMA-directed bispecific data: it looks like prophylactic tocilizumab may be able to help mitigate frequency of CRS with teclistamab and elranatamab. I don't see any reason why we won't be able to utilize the same approach for that FDA-approved BCMA-directed bispecific. I think the real-world data shows that less-frequent dosing is doable and does not impact the durability of response, at least at the 6-month mark after the change.

Combining bispecifics with standard myeloma treatment looks promising, given the depth of response we're seeing in those early cohorts. MajesTEC-7 looks great.

Early-phase trials of the investigational BCMA-directed antibodies look promising. The linvoseltamab data: again, the CRS pattern from that experience appears to be the most impressive out of the lot, but then we have ABBV-383, which is the monthly dosing convenience. A lot is going on in that space, and we're moving to phase 3 trials with these bispecifics.

Josh and Ashley, would you like to add any other key takeaways?

Ms. Steinberger:
I think that what these trials are showing is that these drugs work very well. In the real world, that is what we're seeing; we're seeing people respond quickly and have long responses. Also, these abstracts are pointing to trying to make this safer for patients, easier for patients, and easier for health care providers. So, good things in the pipeline.

Dr. Usmani:
Let's move on and review recent abstracts on non-BCMA–directed bispecific antibodies that were presented at ASCO and EHA.

Dr. Leo Rasche shared long-term efficacy and safety results from the phase 1/2 MonumenTAL-1 study of talquetamab in relapsed/refractory multiple myeloma. As you all know, talquetamab is a GPRC5D-directed bispecific antibody that was approved by the FDA based on the MonumenTAL-1 clinical trial. The approval came about a year ago and was based off the two cohorts of patients who received the 0.4 mg/kg weekly dose of talquetamab. There was a second cohort of 0.8 mg/kg of talquetamab given every 2 weeks. The median PFS reported with the 0.4 mg cohort was 7.5 months and around 11 months with the 0.8 every-2-week dosing. In patients who had triple-class refractory disease, the median PFS was a little less than 8 months. The overall responses were quite impressive. They were in the 60- to 70-odd percent range. It was almost 67% for the triple-class refractory population. Each of the cohorts had almost 55% to 60% of the patients achieving a VGPR or better, so really impressive depth of response. From an adverse event standpoint, I don't think CRS was as significant an issue as were some GPRC5D-associated adverse events.

Ashley, can I get your thoughts on the GPRC5D-specific side effects that we see in clinic? Can you share the talquetamab experience on the clinical trial data as well as your own?

Ms. Steinberger:
People are responding well to this drug, but they have a hard time staying on it because of the side effects. You have to be up front with them at the beginning when they're going on it and tell them what to expect. Personally, what I see most in clinic is the taste changes

and people losing a lot of weight. Usually, when we hold a dose or spread out the dosing, the patient can tolerate it better. There can also be nail changes and skin changes. The skin changes can be peeling on the hands and feet, which will present a little bit later. Also, the nails can separate from the nail bed. There can be nail pitting and also a generalized rash, which I haven't seen as much. But skin, nail, and taste changes are very common with this drug.

Dr. Usmani:
Josh, are there any other safety issues you want to highlight from the MonumenTAL-1 study or with talquetamab?

Dr. Richter:
No, I think overall, Ashley did a great job. I think her assessment of this is really accurate. It's not the easiest drug to keep people on. The way I think about it is that some drugs in myeloma are an ends to a mean and some drugs are a means to an end. And right now, for a lot of the patients, talquetamab is a means to an end to get them to a CAR T, to get them to the next type of therapy.

Dr. Usmani:
And speaking of safety profiles, there is data relevant to infectious complications of bispecifics and CAR T-cell therapies.

Ashley, do you want to comment on some of that new data?

Ms. Steinberger:
As we've mentioned multiple times, infections are one of the biggest things with CAR T cells and bispecifics. There was a retrospective analysis where Julien Mercey and colleagues evaluated infectious complications of any grade in 137 patients treated with either BCMA- or GPRC5D-directed bispecific antibodies or CAR T-cell therapy. Of these 137 patients, 58 were on CAR T, 47 were on a BCMA-targeted bispecific, and 32 received a GPRC5D-targeted antibody. What they saw was that there were less infections in the patients that received the GPRC5D versus the BCMA antibodies. The rates were 76% for CAR T therapy, 85% for BCMA, and 59% for GPRC5D-targeting bispecific antibodies. Most of the infections were viral infections of the respiratory tract. So while talquetamab can cause a lot of other side effects that are unwanted—like the nail changes, the taste, etc.—one thing it does do, is it doesn't put you at as high of a risk as the other bispecifics.

Now we're going to transition over to cevostamab, and Josh is going to cover that.

Dr. Richter:
We saw the CAMMA 2 data presented at EHA by Shaji Kumar. The CAMMA 2 data specifically looked at cevostamab, which is a FcRH5/CD3 bispecific, but the CAMMA 2 data was only looking at patients who had had prior BCMA therapy.

What we saw is early data in a small number of patients. No real post bispecifics in this cohort. It was either patients receiving ADC with belantamab mafodotin or prior CAR T therapy. Overall, the drug is well tolerated. Similar toxicity profile to the other bispecifics, so it doesn't have the nail, skin, and dysgeusia that we see with talquetamab, but it does cause CRS and ICANS at similar rates to the other assets. In terms of infection, if I had to rank them, I think BCMA causes the most infection, GPRC5D the least, and cevostamab is probably somewhere in between, but overall, a fairly well-tolerated drug.

In terms of efficacy, for the entire cohort, we saw an overall response rate of 67%, but this was higher in patients who had prior CAR T rather than the ADC. It was 73% in prior CAR T, 60% in prior ADC. This is really in line with what we are seeing when you even go from BCMA-to-BCMA asset, that the longer the distance in between that attack, the better you do. When you're on an ADC or on it more regularly, the time in between dosing between the ADC and cevostamab was shorter, and that probably impacted the response rate. But overall, response rates were quite high, with about 20% of patients getting VGPR or better. And, again, 73% response rate post-CAR T is really exciting, especially as CAR Ts are moving earlier and earlier. It's exciting that we have some great therapies as salvage when we need them.

Saad, what are your key thoughts on takeaway points?

Dr. Usmani:
I think the long-term efficacy and safety of talquetamab is confirmed based on the longer follow-up that was presented. The points that you and Ashley made about the infectious complications with bispecifics, where BCMA bispecifics rank higher than GPRC5D and cevostamab is somewhere in between. And the CAR T–related infections that we see are actually lower than what we see with the bispecifics. I think it's important to appreciate that. And the early data with cevostamab is in cohorts of patients with prior bispecific and CAR exposure, so I look forward to seeing a little bit more of that data in those cohorts with longer follow-up, because relapsed disease beyond these therapies still remains an area of unmet need, and we have many of those patients in our respective clinics.

In the previous sections, we discussed key clinical trial data that was presented at ASCO and EHA. Let's talk about a patient scenario

and illustrate how to optimize the use of BCMA-directed bispecific therapy in clinical practice.

So, we have a 72-year-old woman with high-risk multiple myeloma. Performance status is 2. At the most recent progression, the patient has amplification of 1q21 along with deletion 17p. In terms of treatment history, the patient started with daratumumab, lenalidomide, and dexamethasone (DRd) as initial treatment like the MAIA trial, but then daratumumab was discontinued and lenalidomide maintenance was continued. VGPR was the best response, but the patient progressed after 1.5 years, then they received a dose-attenuated regimen of bortezomib, selinexor, and dexamethasone, which resulted in a duration of response for about 1 year. Then the patient went back to daratumumab with pomalidomide and dexamethasone for another 9 months or so before progressing. The last line of treatment was a dose-attenuated carfilzomib with cyclophosphamide and dexamethasone, but they only got it for about 5 months before showing clinical progression.

What would be the considerations of treatment for this patient? This is a transplant-ineligible patient, likely being considered for BCMA-directed bispecific therapy here.

Ashley, do you agree? You know, this fourth-line treatment patient whose had all the drugs, but you know, in different doses and schedules probably because of the performance status and not being transplant eligible. What are your thoughts? What are the options for this patient? Would you consider a BCMA-directed bispecific?

Ms. Steinberger:
I think we would, because the performance status is still 2. It's not terrible, so I think we would. We would just need to be careful about giving them, maybe not weekly treatment, maybe every other week. I'm not sure it's selecting between elranatamab and teclistamab. Elranatamab maybe has a shorter hospital stay. I'm not sure if that would be a better option. What do you guys think?

Dr. Usmani:
Josh I'm going to ask if you would treat this kind of patient in the outpatient setting or you would start inpatient and then transition to outpatient?

Dr. Richter:
I think the devil's in the details. I think if the PET scan showed a whole bunch of lesions that were really bulky, I would treat inpatient, but if this is simply a serologic relapse, which it's likely going to be, I think we certainly could treat them as an outpatient. Again, it depends on comorbidities and how much they can tolerate and access a center that could treat CRS, but definitely reasonable.

Dr. Usmani:
Ashley brought up whether to dose them less frequently from the get-go or start weekly and then go less frequent. How would you do it?

Dr. Richter:
I actually kind of approach all BCMA therapy, also belantamab, the same way, which is those initial doses I give on schedule. Once we get the response we need, we back off. I would start with the weekly dosing. The reason is to make sure to keep that is that the prior therapies really hasn't had a deep response, never got those CR MRD-negative responses, so I would really try to eke out a CR or better here, if possible, before switching to less-frequent dosing.

Dr. Usmani:
When trying to modify dosing, Ashley, what would be your biggest concern? Suppose the patient is responding: what are your thoughts around the less-frequent dosing?

Ms. Steinberger:
Less risk for neutropenia and infection would be the reason to back off eventually, once they have a good response.

Dr. Usami:
What's the current dosing schedule for elranatamab at the moment?

Ms. Steinberger:
This is a typical dosing scheduled of where it's given on day 1, 4, and 8. The step-up dose on day 1 is 12 mg, and the step-up dose on day 4 is 32 mg. At MSK, they will be discharged, I believe, at this point, and they come back for the first treatment dose on day 8 as outpatient, and that's 76 mg. After that, it's given weekly up until week 25, where we will switch to every other week.

Dr. Usmani:
So, we have become comfortable dosing patients on days 1, 3, and 5. Just like we did for teclistamab, so that we can transition patients out sooner than later. But we do that on a case-case basis, as well.

Josh, are you guys trying to do that, as well?

Dr. Richter:
Yeah, doses on day 1 and 3, and then 48 hours later, discharged on day 5. I think, assuming the patient is stable without active CRS, we're all kind of taking that approach.

Dr. Usmani:
Instead of elranatamab, with teclistamab what are your thoughts around the dosing and the step-up period?

Ashley, what are the differences, and are they going to be any different? Or about the same?

Ms. Steinberger:
They are similar. The dosing is about day 1, 4, and 7, as well, except the patient is in the hospital the entire time and for 48 hours after the seventh dose. So, day 1 would be—it's dosed by weight—so 0.06 mg/kg, and then day 4, the second dose, is 0.3 mg/kg, and then the first treatment dose is given on day 7, and it's 1.5 mg/kg. That continues weekly as outpatient after that. After day 7, they keep them in the hospital for about 48 hours to monitor for CRS. If there's no CRS and they're stable, they discharge 48 hours after day 7. Also, it's been updated that, for patients who have maintained a CR or better after 6 months, we will reduce dosing to 1.5 mg/kg every 2 weeks. This is the standard dosing, but also step-up doses can be administered between 2 to 4 days after the previous dose, given that the patient is stable and maybe given up to 7 days after the previous dose to allow for resolution of any adverse reactions.

Dr. Usmani:
Josh, what has been your clinical experience with CRS and ICANS in patients who are receiving bispecific antibodies?

Dr. Richter:
As far as CRS, it seems that most people get it. The majority is grade 1 and grade 2, and I think a lot of this has to do with your tocilizumab approach. At Sinai, the minute you spike a fever with grade 1, we pounce on you with tocilizumab. I've spoken to other myeloma experts who have used the phrase, "We let them sizzle a little." I'm not a fan of letting people sizzle. And then once they get tocilizumab, they tend not to have anything else in terms of CRS after.

ICANS, though—even though the rates are very low in the clinical trials, I have to be honest, it's been a little bit higher in clinical practice, and I think this is related to an overall higher burden disease, sicker patients that we're treating with standard-of-care bispecifics than what was done in some of the clinical trials. But still, overall, grade 1, grade 2, most of this is managed across the board. You know, tocilizumab and/or steroids for CRS. For ICANS, usually steroids and occasionally needing to use anakinra. I think if we look at the trial data, we'll see that CRS was the majority of patients, but almost no grade 3 or 4 CRS and really no grade 3 or grade 4 ICANS.

Dr. Usmani:
Ashley, as your patients start treatment with elranatamab, what principles should inform infection prevention?

Ms. Steinberger:
These remain the same, as far as I know, with teclistamab and elranatamab. There are a lot of things that we do to mitigate infections and decrease the risk. The first is to educate the patient and let them know that they will be at a higher risk for infection—tell them to be more careful in certain situations, in crowded areas, to wash their hands frequently, things like that. Just kind of neutropenic precautions. We also, if they are neutropenic, give growth factor, like Neupogen or Neulasta, to help combat that. We will give PJP pneumonia prophylaxis. Whether it's Bactrim or atovaquone or pentamidine, they'll receive one of those to make sure they don't develop PJP. We also will give them acyclovir to prevent shingles reactivation. We monitor hepatitis B, as well, and if they have a positive core antibody, we will likely give them entecavir to prevent reactivation of hepatitis B. Also, we monitor CMV levels to make sure there's no activation of CMV. And lastly, most patients on teclistamab or elranatamab will have to go on IVIg and have close monitoring of IgG levels.

Dr. Usmani:
To summarize the key points from this section, bispecific antibodies as monotherapies are efficacious in relapsed/refractory multiple myeloma. We are seeing early, deep, and durable responses, and these therapies are off-the-shelf. Whether it's a clinical or a biochemical relapse, they're easily accessible for us to utilize in our clinical practices. Overall management strategies that may mitigate CRS and ICANS are important, so early recognition is the key. Tends to happen during the step-up dosing or the first dose of treatment. What's encouraging is that, unlike CAR T-cell therapies, most of the events are grade 1 or 2, and ICANS seldom happens with any of these products. Vigilant monitoring, prophylaxis, and treatment can prevent infections. And Ashley rightly highlighted the VZV and PGP prophylaxis strategies. For patients who may require entecavir for hep B core antigen positivity, these antiviral and antimicrobial strategies need to be continued throughout the treatment. For patients developing hypogammaglobulinemia, IVIg replacement is strongly encouraged.

Let's move on and discuss how to optimize the use of GPRC5D-directed antibodies. We have a patient who is 74. They have a good performance status with an Eastern Cooperative Oncology Group (ECOG) of 1. In terms of treatment history, the patient got VRD as induction, then transplant, and then lenalidomide maintenance. Then, 3.5 years later, the disease was relapsing, so they were switched over to daratumumab with pomalidomide and dexamethasone, and they had a duration of response of about 18 months. VGPR was the best response, even with this line of treatment. The patient went on to have another relapse and received carfilzomib with cyclophosphamide and dexamethasone as their next line of treatment before progressing 1 year later and then being placed on selinexor and dexamethasone for about 4 months before progressing and then received a BCMA-directed CAR T-cell therapy. They remained in response for about a year before progressing, and they're now considered for GPRC5D-directed antibodies with talquetamab.

Josh and Ashley, assuming the patient starts talquetamab, what are the unique side effects that we would need to discuss with the patient?

Josh, maybe we can start with you first.

Dr. Richter:
Any time we're talking about a targeted antibody-based therapy, the question is always, "Where else is that target expressed other than the malignant plasma cells?" For GPRC5D, we know, besides plasma cells, it's expressed on the squamous epithelium of the hands and feet, so dermatologic side effects are something we note. The desquamating rash that people can get actually reminds me of Xeloda back when we used to use more Xeloda. Then there are nail-related issues, where the nails can become brittle or even fall off, or they can become discolored and have ridging.

The other thing is that GPRC5D is expressed in the oropharynx and salivary glands, so dysgeusia, weight loss, anorexia can occur. These are really the big issues that we see.

I think there's a lot of work ongoing to figure out the optimal mitigation strategies. Right now, it's working with a nutritionist, eating small frequent meals, making using things like artificial saliva to help make sure that dry mouth is not an issue.

There's a lot of ad-hoc experimentation lemon and sour or MSG or oral dexamethasone washes.

I would love to know, Ashley, if you have any tips and tricks that have worked particularly well for you with your patients.

Ms. Steinberger:
For the skin-related changes we see a lot of, as Josh said, peeling of the hands and feet. They suggest that patients use ammonium lactate 12% cream twice a day. Also, patients can have more of a generalized rash and, if there's a change, they may need to apply some triamcinolone. Also just adding in any thicker-based ointments, like Eucerin or Vaseline, can help hydrate the skin. Oral antihistamines can be used if there's any generalized itching, as well.

With nail-related changes, as we stated, they can fall off, they become very brittle, they can have nail pitting, or separation from the nail bed. This usually starts around cycle 2 and can last, from what I see, for most of the time that they're on the medication. They should avoid long, frequent durations of water immersion, and they can also apply Vaseline or Aquaphor, vitamin E oil, or nail hardeners, and then Biotin can also help with nail growth and hardening, and then also just filing the nail edges to be smoother.

Other side effects that they can get are dysgeusia and xerostomia. Dysgeusia is the change in taste that people can have, and this is a little bit difficult to combat. Usually, dose modifications of the drug, reductions or delays, or skipping a dose can help with the management of this, and then just telling patients to have things high in calories and to eat small, frequent meals. Also, you need to monitor nutrition, like vitamins, to make sure they're not becoming iron deficient, B12 deficient, folate deficient.

Xerostomia is dry mouth, which also can be seen. Management strategies include increasing hydration and having water throughout the day to keep the mouth moist and using topical agents like saliva sprays or sugar-free chewing gums or candies to help stimulate saliva flow. Patients can use sodium lauryl sulphate–free toothpaste, which might be better tolerated than other toothpastes. But, like Josh said, referring to the dietitian or nutritionist early is encouraged.

We're also going to go over the dosing of talquetamab. Similar to the other medications, there's a standard dosing, but it can be given a little bit earlier if there's no adverse reaction. The standard would be giving it on day 1, and it's body weight based, so it's 0.01 mg/kg on day 1, day 4 is 0.06 mg/kg, day 7 is 0.4 mg/kg, and it's then given weekly thereafter. You would not want to give it earlier than 6 days after the full dosage, the first treatment dose. It can also have a biweekly or every-2-weeks schedule. Similar to weekly in the beginning: it's 0.01 mg/kg on day 1, 0.06 mg/kg on day 4, and then 0.4 mg/kg on day 7, and then the first treatment dose is 0.8 mg/kg on day 10. And then it's given biweekly as 0.8 mg/kg. And in this one you would want to maintain at least a minimum of at least 12 days between the biweekly dosing, but the doses can be administered between 2 to 4 days after the previous dose, if there is no CRS or adverse

reactions.

Dr. Usmani:
The key takeaways from this section: it's very important to educate the patient to be their own advocate. The best prepared patients, as they're starting these new therapies, are going to help mitigate and manage these side effects. They need to know what to look for and how to best reach the health care team. Preparing patients for the possibility of the off-tumor/on-target effects of talquetamab is very important. So, again, repetition is going to be the key here, and patients who know these are common are usually able to cope much better, because they can anticipate what is coming down the pike.

Ashley, any other thoughts?

Ms. Steinberger:
That's pretty much it. If they know what to expect, they're going to be able to reach out and ask for help more easily.

Dr. Usmani:
Any other pearls of wisdom, Josh?

Dr. Richter:
You know the only pearls of wisdom I would say is just ongoing communication with your health care team. We have tools to help mitigate a lot of the side effects of the bispecific antibodies, and you don't get extra points for suffering. Reaching out, because, as a myeloma community, even though these drugs are new, we're all sharing at events like this, where we share our little tips and tricks about how to make the treatment better for everyone. So open line of communication, always.

Dr. Usmani:
Absolutely, Josh. I think, you know that's the case, especially in this late relapse setting where our patients may think, "Oh I'm benefiting from this treatment, maybe I shouldn't tell that this is something happening I may be taken off of treatment." No, that's not the goal. The goal here is to find the right recipe, the schedule and then help manage your side effects as they come along. The sooner we know about them, the more time we have to come up with a game plan with you.

This concludes *Bispecific Antibody Horizons, Dosing Strategies and Meeting Updates in Multiple Myeloma Care*. Thank you for joining us.

Announcer:
Thank you for listening to this episode of *Myeloma Matters* on the latest data on bispecific antibody therapy, hosted by the Multiple Myeloma Research Foundation. We would like to thank Dr. Saad Usmani, Dr. Joshua Richter, and Ashley Steinberger, for sharing their insights on bispecific therapy for myeloma treatment. The Multiple Myeloma Research Foundation also thanks Johnson & Johnson and Pfizer Incorporated for their support of this educational podcast. If you have questions about anything you have heard today, please call the Multiple Myeloma Research Foundation Patient Navigation Center at 1-888-841-6673 for more information.

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