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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

A Roadmap to Safe and Effective Bispecific Antibody Use in Myeloma: Mitigating and Managing Adverse Events

Announcer:
Welcome to CME on ReachMD. This activity, titled "A Roadmap to Safe and Effective Bispecific Antibody Use in Myeloma: Mitigating and Managing Adverse Events" is provided by Prova Education.

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Dr. Costello:
Bispecific antibodies are the newest immunotherapy on the block for relapsed/refractory multiple myeloma. Do you know how to safely integrate these therapies into your practice to optimize clinical outcomes for your patients?

This is CME on ReachMD, and I'm Dr. Caitlin Costello.

Dr. Lonial:
And I'm Dr. Sagar Lonial.

Dr. Costello:
Thank you, Dr. Lonial. Well, to start us off, what can you tell us about the 3 approved bispecific antibodies for relapsed/refractory myeloma?

Dr. Lonial:
Yes, thank you very much, Dr. Costello. And I think what we're really excited about is not just having 1 or 2, but actually having 3 different agents that work through, for us in myeloma, what is a novel mechanism of action. And what I mean by that is we've got teclistamab which targets BCMA, we've got elranatamab that targets BCMA, and then we've got talquetamab that targets GPRC5D. And what we know about these 3 different agents is that their mechanism of action is similar. They are, all 3, bispecific T-cell engagers. And functionally, what that means for patients as well as for providers is that on the one side of the antibody, they bind a T cell, and on the other side of the antibody, they bind a myeloma cell. So they have different receptors on either end. And the net result is that a T cell is brought in close proximity to a myeloma cell, and then goes on to kill that plasma cell.

So this mechanism, again, is not unique in cancer; we've seen this with CD19, particularly in ALL [acute lymphoblastic leukemia] or in lymphoma, but it is relatively novel for us in myeloma. And I would have not guessed it would be as successful as it has been. And yet, as you're going to hear in the next few moments, the data in terms of efficacy is really quite striking.

Now what we really know about this is about their current label, and that is in relapsed and refractory myeloma, after more than 4 prior lines of therapy, including an anti-CD38 antibody, a PI [proteasome inhibitor], and an IMiD [immunomodulatory drug]. So it is relatively late in the disease course. But despite that, the activity has been quite impressive.

Dr. Costello:
Thank you for that wonderful summary. I think you're so right. This has really changed the landscape of treatment for our

relapsed/refractory patients, really

offering opportunities for treatments that historically have really not fared as well as this, as we see with the bispecifics. I mean, we've seen studies that show that these patients who have received monoclonal antibodies, proteasome inhibitors, IMiDs, have median progression-free survival of on the range of 4 months or less with our kind of standard of care options. So what a wonderful opportunity to treat our patients with very effective and increasingly safe drugs as we figure out how to safely administer them.

So thank you for that review, but let's look briefly at the approval of these agents. What were the efficacy data from the pivotal trials?

Dr. Lonial:
Yeah, so let's start off talking a little bit about teclistamab, which was really a small phase 1/phase 2 study called MajesTEC-1. And in that trial, patients with relapsed and refractory myeloma with more than 4 prior lines of therapy, and, in fact, in the trial it was actually more like 6 prior lines of therapy, were enrolled initially in a phase 1 dose escalation and then a phase 2 expansion cohort. And what we saw in that was that the overall response rate was between 60% and 70% and that those responses were occurring relatively early within the first month or 2 and that the responses could be quite deep, in fact, with many patients achieving a complete remission or even MRD [minimal residual disease] negativity in a sizeable proportion of patients in the refractory myeloma setting.

Now, for elranatamab, also a BCMA-directed bispecific, that was actually approved based on the MagnetisMM-3 trial, which was a similarly heavily pretreated patient population, more than 4 prior lines of therapy to get in, again, median of about 6 to 7. And what we saw in there was also a response rate between 60% and 70%, and many of those patients achieved quick responses, with CRs [complete responses] occurring within the first 2 cycles of therapy, and again, deep responses with many patients achieving complete remission or even MRD negativity at 10 to the -5 and 10 to the -6.

The third T-cell engager or bispecific is talquetamab, which targets GPRC5D and was approved based on the MonumenTAL-1 trial. This was a similar trial designed to what I've just told you already, except that with talquetamab, we looked not only at IV and subcutaneous dosing, subcutaneous is what moved forward, but we also looked at an every-week schedule versus an every-other-week schedule for talquetamab. And what we saw was similar efficacy, again, response rates over 70%, quick responses within a cycle or 2, and, in fact, many patients achieved CR and MRD negativity as well.

So those 3 studies really gave us a significant advance for many of our patients, and I think really have helped change the landscape of therapeutic options for relapsed and refractory myeloma.

Dr. Costello:
Thank you for that really nice overview. I think you and I both remember that single-agent approvals by the FDA historically have always been on the range of overall response rates about 20% to 30% when looking at some of our historical drugs, pomalidomide, lenalidomide, daratumumab, carfilzomib. So to see drugs now, for our patients who are most in need, be approved with response rates, as I think of what you describe for these 3 different drugs of 60% to 70%, really moves the bar. We are seeing these patients who are in such dire need of treatments have great treatments now that are more effective than drugs we've ever seen kind of treated or evaluated in this same setting.

And this is going to become important and extremely relevant as we've seen the kind of landscape of myeloma change, where now we have our usual suspects of drugs that we're using in greater combinations with 3-, 4-drug combinations very early on in the disease, where we really are going to need our next new candidates for treatments. Although now approved for later-line therapy, I think we both know that this is probably going to be seen to be moved forward to kind of earlier relapses just the same.

For those of you just tuning in, you're listening to CME on ReachMD. I'm Dr. Caitlin Costello, and here with me today is Dr. Sagar Lonial. We're discussing the safe and effective use of bispecific antibodies in the treatment of relapsed/refractory myeloma.

All right, let's switch gears. I want to talk a little bit about the safety profile of these bispecific antibodies. We've talked about efficacy, but what about safety? Can you tell us a little bit about the cytokine release syndrome, or CRS, and the neurotoxicity that's related to these agents?

Dr. Lonial:
Yeah, that's a great question because it is a relatively new mechanism of action for us. In plasma cell disorders, you might be concerned that the adverse events would be a little bit different, but in general, it's not dissimilar from what we see for CAR T cells in that, as you just described, CRS and neurotoxicity are somewhat prominent adverse events that we see.

What I think about, though, is that, on average, both the BCMA- and the GPRC5D-directed bispecifics are 1 grade lower than what we see with BCMA-directed CAR T cells for both CRS and neurotoxicity. So I think of it as a spectrum; the highest incidence of both of these occurs in the context of CD19 CARs, for instance. I think BCMA CARs are 1 grade less than what you see for CD19 CARs. And I think

that bispecifics are, on average, 1 grade less than what we see with BCMA-directed CAR T cell. So certainly mostly grade 1/grade 2 for both.

Now, it is important that there is a REMS [Risk Evaluation and Mitigation Strategy] program for all 3 of these agents. Because if you don't have experience in anticipating or treating CRS, that is something that is probably necessary not just by you as the provider, but by your multidisciplinary team because we know if these drugs are given, for instance, during the day, some of these side effects may occur at night or not during regular office hours.

Now, CRS occurs roughly 60% to 70% of the time, mostly, again, is grade 1/grade 2, higher in patients with high tumor burden or more refractory disease. And the management strategies for this is often tocilizumab, or toci, and can, in some situations, require corticosteroids.

Now neurotoxicity is a little different. Again, this can often present with word-finding or writing difficulties, but at its most extreme, can present with obtundation or really loss and confusion and altered mental status. Now typically, neurotoxicity will occur in the context of CRS, although it does not have to. And neurotox does not seem to respond as easily to tocilizumab alone, and so we typically consider things like corticosteroids in patients like that as well.

And then, again, generalized supportive care is indicated for management of these patients as well, because they do tend to be pretty sick. They're usually in the hospital for most of the management of these situations. And again, you need to have a team that's prepared to handle, be aware, and manage both of these unique T-cell engager-associated side effects.

Dr. Costello:
You're so right. With new drugs come new toxicities that we all have to learn, and thank you for touching on those so nicely. I think the CRS, you mentioned beautifully, is really being aware of these patients having very immunocompromised states, right? So when you see those fevers, we've got to make the assumption it's CRS, but don't forget that these patients are at high risk for infections and go through the same usual protocols, evaluating for infections as well. Neurotoxicity, just the same, very specific criteria to evaluate and know when to intervene. So the multidisciplinary approach is so necessary.

Okay, so thank you for that. But what do you think are some of the other treatment-emergent adverse effects we need to watch for when using bispecific antibodies?

Dr. Lonial:
Yeah, and I think you hit on one of them before already, which is infections. But what we know is that not only are these patients at risk for infections because of their prior therapy and how heavily pretreated they are, we know that targeting BCMA also seems to increase the risk of infectious complications. And so aggressive monitoring, prophylaxis, support for neutropenia, if present, those are all things that are really critically important. And those include prophylactic antibiotics in some situations, prophylactic antivirals, checking for viral infections particularly if you see pancytopenia developing. And, I would say, telling patients to have a heightened sense of awareness that, whereas in previous treatments, they may have said, "Well, no, I don't feel quite well but I'm going to try and ride this out," in somebody receiving a bispecific, you don't want to take that approach, particularly if it's targeting BCMA, because these infections can sneak up on you and they can be quite severe. But with appropriate dose modifications and supportive care, for the most part, they can be mitigated or minimized or treated early.

Now, a unique adverse event for the GPRC5D-targeting agent is skin, oral, and nail adverse events. And those are, unfortunately, at least right now, seem to be associated with a higher response rate. And so I don't think it's a matter of maybe you'll get it, maybe you won't; I think patients who do get these toxicities are more likely to get a deep and durable response. And so I think understanding how to manage patients with these adverse events is really critical. It may often require topical therapy on the skin or in the mouth; it may require holding doses or reducing doses; these are all very key as well. Typically, the symptoms will maximize in the first cycle or 2 of therapy, and then you'll see a reduction over time. Whether that's because you sort of burn out these side effects or you make dose adjustments or dose holds, I think, is unclear. But I think partnering with dermatologists potentially might be one way to help manage some of this as well.

And then again, more importantly, making sure you're supporting cytopenias like neutropenia or thrombocytopenia, making patients aware ahead of time. We do – I'm sure you do as well – a fair amount of education before they even get a dose so they know what to expect. And those things can reduce the risks of complications for patients overall.

Dr. Costello:
That was a beautifully thorough explanation of this. It is complicated, but with partnering with our patients, with our multidisciplinary approaches, we really can make this very safe.

I think the only thing I would add to that is – I think you didn't mention, but I think I know you do – is intravenous immunoglobulin [IVIG]. I think it's just so critical with all those antivirals and antibiotics to do the best we can to prevent. But IVIG has a big role for these patients who are just so severely hypogammaglobulinemic, their T cell compartment is wiped out because they're doing all the hard work against the malignant plasma cells, so don't forget those as well.

Well, this has been a fantastic conversation. Before we wrap it up, Dr. Lonial, do you have any hot tips or any take-home messages you want to leave our audience with?

Dr. Lonial:
Yeah, and I think it really goes back to what you said at the very beginning; these are such fantastic and effective agents, I don't think we want people to be afraid to use them. And so partner with a provider, a team, a center that has used this a fair amount, learn from those centers, use them as a resource, and recognize that once you get past the first few doses, most of the treatment-specific adverse events tend to go away. And it's really only the things we talked about, such as infection risk or skin or oral complications, that may perhaps persist. But the risk of CRS and neurotoxicity is vanishingly small once you get past the first few doses. So if you're partnering with a major myeloma center to give this, know that by the time they come back to you, that risk is pretty small.

Dr. Costello:
Well, thank you so much, Dr. Lonial. That's just about all the time we have for today. I want to thank our audience for listening in and to you, Dr. Sagar Lonial, for joining me and sharing all of your valuable insights. It was great speaking with you today.

Dr. Lonial:
Thank you.

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