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Cracking the CRS Code in Myeloma: Insights from a Comprehensive Case Review

Announcer:
Welcome to CME on ReachMD. This activity, titled "Cracking the CRS Code in Myeloma: Insights from a Comprehensive Case Review" is provided by Prova Education.

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Chapter 1
Dr. Costello:
Welcome to this educational series on managing cytokine release syndrome, or CRS, related to bispecific antibody therapy for relapsed refractory myeloma. In this first chapter, we're exploring treatment options for a patient with penta-refractory multiple myeloma in a case-based discussion.

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

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

Dr. Costello:
I'm so glad to be here with you today, Dr. Lonial. Let's get started.

Let me present a case to you of a patient named Robert. He is a 75-year-old man who you've been following for his IgG kappa myeloma for the past 9 years. He comes back to clinic to you now, and you all have decided that he has relapsed, unfortunately, with his myeloma. You're discussing his prior therapies, and those include a stem cell transplant, he's had 2 different proteasome inhibitors, 2 different immunomodulatory drugs, and an anti-CD38 monoclonal antibody. Now, at the ripe age of 75, he has comorbidities, including hyperlipidemia, but it's well controlled with his diet and exercise and atorvastatin 10 mg daily. He has a good performance status of 1.

Now, Dr. Lonial, what are the treatment options for this patient?

Dr. Lonial:
So when we think about a penta-refractory myeloma patient, what we think about is what are the potential different new mechanisms that this patient has not been exposed to that might offer clinical benefit? And probably the longest approved of those agents includes a drug called selinexor in combination with dexamethasone. Most recently, what we have now are CAR T cells and bispecifics. And those include targeting for the CAR T cells, BCMA; and for the bispecifics, targeting BCMA or GPRC5D.

And when you think about which of these available FDA-approved regimens to use, there are a number of factors that go into that discussion, including what are some patient preferences, what adverse events has a patient already had prior to coming to this treatment approach, which data perhaps gives us the highest efficacy with the best safety profile, and/or which has the longest progression-free survival [PFS], particularly in the relapsed and refractory setting? And before we had the availability of CAR T cells and bispecifics, we would be happy with a response rate of about 30%, and we'd be happy with a median PFS of between 3 and 6 months. And as we're

going to discuss in the coming moments, that is not the case any longer, particularly with the availability of T-cell engagers or bispecific antibodies.

Now, as we begin to decide one agent, one approach versus another, there certainly are some things that patients and their families need to be aware of because there are some unique toxicities, particularly to targeting BCMA or targeting GPRC5D and making sure that patients have the support and resources to be able to deal with that, as well as the knowledge to be able to deal with that, really is a critical part of the discussion that may drive treatments down one avenue versus another in this context.

Dr. Costello:
That is a wonderful approach to selecting treatments for our patients. And, you know, I really like to break it down to think about the drugs that the patients have previously had, any toxicities that they may have incurred from that that are still residual, thinking about the biology of the disease, and then thinking about the patient themselves in terms of comorbidities, but just as you outlined, social support. I think at every relapse in a patient's journey with myeloma, whether it's early on in the disease course or later on, we're going to always be considering those specific criteria when we're making any decisions.

This has been great. Before we wrap up, Dr. Lonial, do you have a key takeaway from this chapter you'd like to share?

Dr. Lonial:
Thank you very much, Dr. Costello. And I think our discussion has really framed this in a really unique way. And what I want to really finish up with is a point that you hit on just a moment ago, which is we have, clearly, very active agents. And one of the things that I struggle with is when patients come back to me, recycling the same old 4 or 5 different drugs that they've seen in the past. And what we know about that is that it's not likely to offer significant benefit, and it is likely to offer significant toxicity. So I think in this new, modern era of myeloma therapy, it behooves all of us to feel comfortable with using these new targets and new classes of drugs to really optimize outcomes for patients.

Dr. Costello:
Thank you. In Chapter 2, we'll be discussing practical considerations for bispecific antibody therapy for the treatment of relapsed refractory multiple myeloma. Stay tuned.

Chapter 2
Dr. Costello:
Welcome back. Now we're moving on to practical considerations for the use of bispecific antibody therapy. Let's get started.

If you remember, in the first chapter of this series we met Robert, a 75-year-old man with heavily pretreated relapsed refractory myeloma who was diagnosed 9 years ago. After discussions with Robert and his caregiver, Robert opts for treatment with a bispecific antibody.

Dr. Lonial, what are some of the practical considerations that need to be addressed when preparing a patient for bispecific antibody therapy?

Dr. Lonial:
Yeah, thank you very much, Dr. Costello. And I think this case really is a pretty commonly seen case, unfortunately, for many of us that treat patients for a long period of time. And in this case, having exhausted most of the available big 3 options, if you will, choosing a bispecific antibody in this context, I think, is a good choice.

So the first thing that I do after I sort of outlie the potential treatment options and approaches, is to really begin talking about scheduling the admission for the initial or step-up dosing of the T-cell engager, and talking about when we can do that and what the time frame will likely be for that context as well.

And in the first steps of doing this, I will typically have my PharmD come in and spend about 20 minutes or so with the patient and their family, going over what to expect, what the potential side effects are, the time that they'll be in the hospital, what some of the medications we may use to manage or support the patient during their hospital stay, and other issues that are typically more sort of nuts and bolts about how do we give a T-cell engager. In addition, we'll talk about premedications. And typically, for that discussion with the PharmD as well as with the nurses and the APPs that are part of our multidisciplinary team, we'll also have an extensive discussion with the family, because you do need a caregiver. And oftentimes they need to be educated on what are the potential things that you need to be looking out for, what do you need to be aware of, and what do you need to know how to do yourself?

And many of these patients will have undergone a transplant in the past. And so some of the – you need to live close to us for the beginning, we need to make sure that you've got a thermometer at home – all those kinds of things are relatively straightforward, but some of them may need some tuning up. And particularly talking about some of the adverse events that occur with the first few doses of

a T-cell engager. Making sure that patients are well educated so that they can anticipate some of those events, I think, is really critically important as well.

Now, if you've not given a T-cell engager, there is a real important need for collaboration between the team and the hospital managing these patients, as well as your office or major myeloma centers that are delivering specialty care in a way to try and mitigate the short- and long-term potential effects of both CRS and potentially neurologic toxicity.

And so making sure that everybody's on the same page, that everybody's had that kind of important education is a way to try and minimize surprises, which are the worst when patients are in the hospital, as well as to try and guarantee that seamless transition between the outpatient to the inpatient and then back to the outpatient for subsequent care.

Dr. Costello:
I couldn't agree more. You really aptly described this as a team sport, which it truly is, between the patient, their caregiver team, you the physician, your supporting staff, the nursing staff, the pharmacist, everyone has an important role in this. And that is true in the hospital where you may include some of your other multidisciplinary colleagues, including neurology, as an example, your infectious disease colleagues, and for patients outside of the hospital, as we start to create the infrastructure to treat these patients outside of the hospital as well. Everyone has a very specific role, which is most critical, I would argue, during the initial step-up dosing. Once everyone's got the hang of it, then it seems to be a little bit more in cruise control thereafter.

Well, this has been great. Before we wrap up, Dr. Lonial, what's your one key takeaway from this chapter?

Dr. Lonial:
Well, yeah, I mean, I think you brought it up: get your team together early, realize that this is not a lone gunman situation. You've got to have everybody around you, and they need to be ready when that first patient gets dosed.

Dr. Costello:
Well, thank you. In Chapter 3, we will be discussing the management of bispecific antibody-related cytokine release syndrome. Stay tuned.

Chapter 3
Dr. Costello:
For those 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 best practices for the identification and management of cytokine release syndrome, or CRS, related to bispecific antibody therapy in patients with penta-refractory myeloma.

Welcome back. Now, we're exploring best practices for the identification and management of treatment-emergent CRS. So let's get started.

In Chapter 2, after you discuss treatment options with Robert, he chose treatment with a bispecific antibody therapy. Robert was monitored for treatment-related toxicities and unfortunately developed signs and symptoms of CRS on the second day after treatment.

Dr. Lonial, how would you manage the CRS?

Dr. Lonial:
Yes, thank you very much, Dr. Costello. And I think this is something that people do need to be aware of in terms of timing and understanding how to do this. And as we know, with that first dose, which is a really, really small dose of the bispecific antibody, it's uncommon but certainly possible that one could have CRS after that first dose of therapy. In fact, I had one patient that their CRS was so bad, they didn't want another dose ever again. And they ended up in a response for almost a year with just that single step-up dose. But typically, we will see signs or symptoms of CRS after dose number 2. And the keys are to be aware of what may be coming. So again, the staff needs to be aware of what's going on.

And typically, we'll manage CRS with a medicine called tocilizumab, which is an anti-IL-6 antibody. Now, this is really important because, A, your pharmacy needs to have tocilizumab on board if you're ever going to treat a patient with a bispecific antibody. And at the same time, the training and experience of your team really is the reason why the REMS [Risk Evaluation and Mitigation Strategy] program is really so important.

And then management strategies for CRS, at least in my view, if you can find ways to reduce the tumor burden before a patient receives that first dose of a treatment, then likely the incidence or severity of CRS may be lower overall. And when we talk about symptoms of CRS, what we're really talking about is fever, potentially hypotension, potentially hypoxia requiring nasal cannula or more intensive support, and at its most severe, it can look like severe sepsis with multisystem organ failure. Fortunately, in the context of bispecifics in

myeloma, that's a relatively rare event. And so most patients will typically have grade 1 or grade 2 CRS that can be addressed with tocilizumab.

Now, Dr. Costello, I just want to push this back to you for just a quick second and ask you what else do your center or do you worry about when somebody presents with fever, hypotension, and potentially needing oxygen with fifth-line myeloma therapy while they're in the hospital?

Dr. Costello:
Great question. And I think all of what you've described is what we presume is happening. CRS, we know, is most common during that step-up dosing. But don't forget that these patients are highly immunocompromised. After 5 lines of prior therapy and in the midst of getting bispecific therapy, you have to assume to some degree there's an infection until proven otherwise. So along the same lines as we are evaluating for CRS, we are making assumptions about infections and will undergo the same approach, such as blood cultures, urine cultures, chest X-rays, you know, all of those are important, empiric antibiotics. Just as you mentioned, these patients look like they could have impending sepsis and they very well may, but probably more likely they have CRS. So kind of think about both of those things at the same time.

As far as the monitoring of the ICANS goes, you know, there is very specific criteria after these patients have had CRS, or can be completely independent of that. Sometimes these patients can develop headaches or ICANS [immune effector cell-associated neurotoxicity syndrome], which is more of a neurotoxicity. We have very specific criteria for evaluating these patients objectively that sometimes even only family members will pick up kind of subtle changes. But we can pick up changes in how they're thinking, mechanics, motor skills, how they're writing, for example, vague, very gentle signs of confusion, of disorientation, for example. And so it's very important, we think, to partner with the caregivers to make sure that we are evaluating these patients carefully for signs of neurotoxicity.

Dr. Lonial:
I think you've really nicely summarized sort of all the things that need to be going on in your head. And it raised a thought in my mind as well, which is patients that have recently had infections, you want to make sure that those are really knocked out before you potentially treat them. And some of that, obviously, is the intrinsic immunosuppression associated with these kinds of treatment.

But the other is if you've got sort of a heightened and activated immune system, because a patient may have had pneumonia 4 days ago or something like that, they're going to be more likely to potentially have CRS as a complication because their immune system is sort of primed before you're even starting. So making sure you give appropriate interval between the last infection, if a patient had one, and when you're planning to treat with a T-cell engager, I think is another thing to just keep in the back of your mind.

Dr. Costello:
I think the last thing I would add to that is something you touched on, the importance of having access to tocilizumab. We cannot do this treatment without it. And it begs the question to say, well, when is the right time to use it? And I think you and I would both argue that we've historically waited a bit, but I think we're understanding now that we don't have to do that. We know that maybe we can intervene on these patients early in their course of CRS or perhaps to prophylax against, as well. So I think there's exciting things to come to help mitigate some of the CRS that we've seen.

Well, that is all we have for today. I want to thank our audience for listening in and thank you, Dr. Sagar Lonial, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Lonial:
Thank you.

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