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Maximizing Myeloma Outcomes With GPRC5D-Directed Therapy: Practical Expert Case Studies and Best Practices

Dr. Matous:
We are in an exciting era for T-cell redirection therapies in multiple myeloma. While there are several BCMA-targeting bispecific antibodies and CAR T-cell therapies available, talquetamab stands out as the only approved therapy targeting GPRC5D.

This is CME on ReachMD, and I'm Dr. Jeff Matous at the Colorado Blood Cancer Institute in Colorado, part of the Sarah Cannon Research Institute.

NP Catamero:
And I'm Donna Catamero, an oncology nurse practitioner and associate director of multiple myeloma research at Mount Sinai Hospital in New York City.

Dr. Matous, what makes GPRC5D an important target in the evolving landscape of T-cell redirection therapies for treating multiple myeloma?

Dr. Matous:
GPRC5D is an interesting target for several reasons. First of all, it's expressed primarily on a plasma-cell phenotype with little or no expression on normal B-cells, normal T-cells, NK-cells, monocytes, granulocytes, or bone marrow progenitors. So this distinguishes it, for example, from targeting CD38 or BCMA.

Furthermore, we know that we have clinical data now from several studies, primarily the MonumenTAL-1, the pivotal trial, which examined the use of talquetamab, which is a bispecific antibody binding both CD3 and GPRC5D. And in the MonumenTAL-1 trial, patients with relapsed or refractory multiple myeloma were enrolled and there were about 140 patients enrolled. They had a median of five prior lines of therapy; 1/4 of them were penta-refractory, 1/3 of them had high-risk cytogenetics, and in the MonumenTAL-1 trial, I should add that 2 different doses of talquetamab and 2 different schedules were explored. One was the 0.4 mg/kg weekly; of course, this is after the step-up dosing. And the other cohort was 0.8 mg/kg every 2 weeks. Across the board, their response rates were good. They were in the 2/3 or higher range. The responses were deep. They were durable.

And what I think is really exciting, as well, is that we have 3 GPRC5D-targeting CAR T-cells in development, and we're seeing more and more data at our meetings come out with those. And I think they'll have a role in the future treatment of our myeloma patients.

So, Donna, how does the safety profile of talquetamab compare to those of the BCMA-directed bispecific antibodies such as teclistamab and elranatamab?

NP Catamero:
So, similar to BCMA-targeting therapies, we anticipate CRS and to a much lesser effect neurotoxicities. However, talquetamab, we do see a lower incidence of infections and, more importantly, we see less serious infections. And these are the types of infections that are requiring IV antibiotics or lead patients to being hospitalized.

We do, however, see more on-target, off-tumor side effects, so we see skin and nail side effects, oral toxicities, such as dysgeusia,

dysphasia, and dry mouth.

Because these are very unique side effects, we take a multidisciplinary approach to manage these toxicities. We really want to help keep patients on treatment.

Dr. Matous:
So, Donna, let's start with our first patient case.

So our first case is a 65-year-old Caucasian female who's referred of May of this year, 2024, for relapsed/refractory IgG kappa symptomatic myeloma, which was initially diagnosed in 2015. Her disease was characterized by an 11;14 translocation, deletion 13q, and trisomy of chromosome 5.

She was induced with VCD back then and referred for high-dose melphalan 200 mg/m2 and stem cell transplant. After that, she went on maintenance therapy with lenalidomide. She went through a series of relapses: the second-line therapy was DPd, or dara/pom/dex.

Third line, she received KCD, carfilzomib, cyclophosphamide, and dexamethasone, then her fourth-line therapy was belantamab mafodotin, which was poorly tolerated.

So after this, she was referred for fifth-line talquetamab. She received her first step-up dose in May of 2024 and was on the bi-weekly dosing schedule. By day 22 of cycle 1, she had noted dysgeusia and mild burning when she ate or drank anything acidic. And she also experienced anorexia and a weight loss of 5 pounds.

Donna, how would you manage the oral toxicity associated with talquetamab in this situation?

NP Catamero:
So, unfortunately, I don't have that silver bullet therapy that will eliminate all these oral toxicities. But we can provide patients with supportive care measures to, again, help them stay on treatment.

So in my practice, with the initiation of therapy, I'm adding in some oral rinses for patients. So I'm prescribing patients a dexamethasone swish and spit and a nystatin swish and spit. And I'm asking patients to do this 3 times a day. In addition, because we see the dry mouth, we're adding in saliva substitutes, such as a sodium chloride-based mouth rinse. And we're asking patients to do this every 4 hours while they're awake.

And then, for patients, because I'm really concerned about the weight loss, and we know that these oral toxicities can greatly affect a patient's quality of life, I add in a nutritional consult. Really, I have them seen during that step-up dosing because we're going to probably need to make some dietary modifications, so we want to make sure that patients have high-caloric, high-protein diets so that we can avoid the weight loss. And then, especially if a patient is having that dry mouth or difficulty swallowing, we will need to do those dietary modifications.

Education is important for patients. So we need to set those expectations that this most likely will occur and then how we're going to manage it. And really, compliance on some of these supportive measures is important, and it will help patients manage some of these oral toxicities. And again, it can be challenging, but I think with good education and support, patients can get through this.

Dr. Matous:
I couldn't agree more, Donna. I think it's super important to really educate our patients prior to starting talquetamab just so that, again, to set expectations, and let them know that if they get significant dysgeusia or oral toxicity, that we, down the road, have remedies that we can institute with dose modifications, if necessary, and often with a lot of success. And I found in practice that just over time, sometimes, some of these side effects just improve with a steady dosing.

Dr. Catamero:
You touched on dose modifications, and I really think this is what helps patients the most. If we can get patients into a good response, and they're experiencing these side effects. Studies have shown that we can, maybe, titrate the dose or the frequency for the tolerability, and I think patients maintain that response, and we have some resolution of these side effects.

Dr. Matous:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Jeff Matous, and here with me today is Donna Catamero. We're discussing best practices to incorporate GPRC5D-directed therapies in the treatment paradigm of multiple myeloma.

Perfect. So let's go on to our next case then.

So this case is that of a 71-year-old male, diagnosed in March of 2016 with IgG lambda ISS stage 2 symptomatic hyperdiploid myeloma. So he went on the ENDURANCE protocol, which was ECOG E1A11, and was randomized to the KRd or carfilzo/len/dex arm. And

elected on that arm to go to up front transplant, which he received in July of 2016. So we got the usual melphalan 200 mg/m2, stem cell support, achieved stringent first CR, and went on maintenance lenalidomide. So that's line number one.

He relapsed in 2021 and received elotuzumab, pomalidomide, and dexamethasone and got about 8 or 9 months out of that. And then progressed to third-line therapy and received daratumumab-VCD for one cycle, and he progressed very rapidly on that. So the fourth-line therapy was selinexor, carfilzomib, dexamethasone; then he got just about 6 or 7 months out of that before he progressed again.

So the patient enrolled on MajesTEC-2 with teclistamab combined with an experimental medication called nirogacestat, and he went on study in February 2023. Responded but chose to come off due to intolerance of nirogacestat in October 2023, and unfortunately, by early 2024, he was progressing again. And he went on sixth-line therapy at this time with talquetamab.

At about 6 weeks, he developed palmar-plantar erythema that progressed to mild desquamation. So we had peeling skin on his palms and soles, mild erythema, and tenderness.

And so, Donna, how would you manage skin toxicities in this type of situation?

NP Catamero:
I think these dermatological toxicities are a little more easily managed. And they tend to be self-limiting. So first thing that we see is dry skin, and so what I counsel my patients on is, again, with the initiation of therapy, I'm not going to wait till someone has a side effect, so I advise patients to use those heavy moisturizers, those barrier creams.

With the hand-foot peeling, what I will prescribe for my patients is ammonia lactate 12% lotion, and I'm asking patients to put that on the soles and the palms and do that twice a day for that skin peeling. And these will typically resolve in several weeks with these interventions.

We also see some nail thinning and peeling. What I advise patients to do is use those nail hardeners, some topical vitamin E oil, or cuticle oil. If I see that the cuticle is getting infected, we'll add in an antibiotic ointment to make sure that we don't see infections on the nail bed.

We can also see some generalized body rashes or injection site reactions, so with injection site reactions, we're going to do a topical steroid ointment, and if there is pruritus with that rash, we can add in loratadine for several days. And for a generalized body rash, we'll add in a steroid taper.

So if these rashes or dermatological toxicities, if we consider this severe or a grade 3, we're going to hold the dose until these toxicities resolve. And then consulting with dermatology can be helpful, and I recommend doing that early on to help manage these patients.

Dr. Matous:
Perfect. So let's go on to our third case. This is a fifth-line patient here.

So 57-year-old woman with relapsed/refractory myeloma, diagnosed 6 years ago, was enrolled on MonumenTAL-2. MonumenTAL-2 had many different cohorts exploring different combinations of talquetamab. And this is a cohort combining pomalidomide and talquetamab for, in her case, recurrent IgG lambda symptomatic myeloma. Now, when she came to treatment, she had pretty significant disease burden. And so she received her first step-up dose of talquetamab on December 1, 2021, and the second dose 2 days later, and then the first full dose 3 days after that.

But after her first step-up dose, she developed a temperature of 40°C. Importantly, she did not have any hypotension or hypoxia, and she received a single dose of tocilizumab, and the CRS never recurred. She went on to have pomalidomide added to her talquetamab, there were no further CRS events noted.

And so this is a patient who developed cytokine release syndrome and, Donna, how do you manage it?

NP Catamero:
So cytokine release syndrome, or CRS, is quite common with all bispecifics, CAR-Ts, so this is anticipated. And we talk about step-up dosing. We also are going to premedicate patients with acetaminophen, and a steroid.

And typically, this can take place as an inpatient, but more and more institutions are actually feeling more comfortable doing this as an outpatient. Because as we're using these therapies, I think we're getting very comfortable at managing this type of side effect.

And our staff is very good at recognizing the signs and symptoms of cytokine release syndrome, and it typically will present as a fever. And at our institution, we give tocilizumab right away. So we're going to try to prevent this from getting any worse with hypoxia or hypotension.

And so we've been pretty successful at keeping the CRS at a grade 1, which, again, is a fever. And so, hopefully, we'll get more and more comfortable with this, that we can do this as outpatient, and this will be more accessible for patients.

Dr. Matous:
I talked to our colleagues around the country. All types of different strategies are being employed, from the prophylactic tocilizumab. You're not waiting for grade 2 CRS, if you see that fever, you're dosing patients with toci, and I think that's pretty common these days.

We do have our patients take a little acetaminophen and dexamethasone. If they're not feeling sick, then we assess them in the clinic to get them their tocilizumab more often than not. I think that the CRS, when I talk to my community colleagues, is the one thing that gives them pause, right? That's something that makes a lot of physicians in the community hesitant to adopt bispecific therapy.

So this has been a great conversation, but before we wrap it up, Donna, can you share one take-home message for our audience?

NP Catamero:
So with these bispecific therapies, talquetamab, we're seeing such great efficacy for patients. So if they're having these oral side effects, these dermatological side effects, my job is to make this as manageable as possible because I want to keep that patient on therapy for as long as possible so that they can really see those overall outcomes that we see on studies.

Dr. Matous:
I think in the future patients are going to be exposed to BCMA-targeting agents and GPRC-targeting agents. And so there's an art to administering a GPRC5D-targeting agent, and you've addressed that beautifully today.

That's all the time we have today, so I want to thank our audience for listening in. And thank you, Donna, so much for joining me and sharing all your incredibly valuable insights. It was great speaking with you today. Thank you very much.

NP Catamero:
Again, thank you, Dr. Matous, for having me. This was a great conversation. Thank you everyone.