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Novel Clinical Approaches in Multiple Myeloma: CAR T Cell Therapy

Announcer:
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Dr. Lonial:
It's an exciting time in the care of patients with refractory multiple myeloma. These are patients who historically have had limited options and poor outcomes. We now have treatments for these patients like CAR T cell therapy, where you reprogram a patient's own immune system to target and kill their myeloma.

This is CME on ReachMD, and I'm Dr. Sagar Lonial.

Dr. Raje:
And I'm Dr. Noopur Raje.

Dr. Lonial:
We're fortunate to have a great target for CAR T cells in myeloma: B cell maturation antigen, or BCMA. Using this target, we now have 2 FDA-approved CAR T cells for our patients. How did we get here, Noopur?

Dr. Raje:
As you pointed out, Sagar, we are fortunate to have this really good, validated target, BCMA. This is specifically expressed on multiple myeloma cells, and we also know that BCMA helps with survival of these myeloma cells, making it an ideal target. We now have 2 large clinical trials, which got 2 CAR products approved, the KarMMA trial and the CARTITUDE-1 study.

The KarMMA trial. This was getting idecabtagene vicleucel approved. And this was based on studying 128 patients. They started off with 4 different dose levels; the recommended dose level is 450 million cells. And what you see with this data set is a very high response rate to the tune of 80% when you look at the 450-million cell cohort, and this resulted in a complete response [CR] rate of about 39% to 40%. And those patients who achieved a CR ended up with a progression-free survival of close to 22 months.

Now looking at the CARTITUDE-1 study with ciltacabtagene autoleucel, this was studied in 97 patients. And again, with this CAR T cell in a pretty heavily pretreated patient population, you're seeing very high response rates to the tune of about 97%. The CR and MRD [minimal residual disease] rates in this patient population was a little bit higher. And just recently, we saw updated results of cilta-cel, wherein we are seeing a progression-free survival at 2 years of about 72%.

Dr. Lonial:
When you look at these very heavily resistant patients, what we saw in both of those trials was very deep responses with some patients achieving MRD-negative complete remission. And that's MRD even as deep as 10 to the -6.

If you look at those patients in particular, they seem to have really long durable responses with both products. From the most recent update of the CARTITUDE trial, the median PFS for all patients is somewhere around 2 years as opposed to about 12 months with the KarMMA study, but the CR patients are doing quite well in both of them.

The one area where I think we clearly need to make additional improvements is in patients who have extramedullary disease, and I will give credit to both of these trials that they really look at those patients in depth. Particularly doing pre- and post-treatment PET scans to better understand what proportion of these patients actually had extramedullary disease and what proportion of these patients ultimately ended up responding with durable responses. Patients with this extramedullary component may have gained less of a benefit. But in general, seeing those deep and durable responses in a group of patients with a median of 7 prior lines of therapy really was remarkable. I know you saw this too, Noopur, when you had a patient who, within 24 hours of getting their infusion of the CAR T cell, you could see a plasmacytoma on their head or somewhere else in their body shrinking in real time. That was just amazing for us to see as clinicians.

Dr. Raje:
Absolutely. You know, I would never have imagined it to have worked in sort of end-stage myeloma. And these patients who were included on these trials were patients who had basically had at least 4 lines of treatment for both CAR T cell products. That is the current indication. So most of them have seen both proteasome inhibitors, bortezomib, as well as carfilzomib. They've seen both of those immunomodulatory drugs, lenalidomide and pomalidomide. And the majority of these patients had seen anti-CD38 monoclonal antibody.

And if you look back, Sagar, at patients who've had prior anti-CD38-based treatment and then have relapsed following this, we've seen that the median duration of response is around 3 months, and the median survival of these patients is certainly less than a year. So obviously, with these CAR T cell products, we are seeing a completely different sort of response rates and durability of response as well.

I do want to mention, there is a waiting period wherein you collect the cells, you actually manufacture the CAR product, and then get the patients back 3 or 4 weeks later on to give them these CAR T cells, wherein we give them lymphodepleting chemotherapy. It does require working with the referring oncologist and really planning out the treatment of these patients so that we can try and get them to that CAR T cell product.

Although the indication right now, Sagar, is 4 prior lines of treatment and have been exposed to all of the drugs that I've just mentioned, after you look at this data set and based on your clinical experience, which patients do you think are candidates for CAR T cells?

Dr. Lonial:
That's a great question. Those of us who've seen these kind of dramatic responses, and that the adverse event profile is easier in many ways than so many other treatments we have, one of the first comparators we think about is with patients who could potentially go through a transplant. So is it as intensive as somebody going through high-dose therapy and autologous transplant? Do we have similar kinds of criteria for who should or should not be considered?

In our experience, I think our oldest patient who's gotten a CAR T cell for myeloma is in their 80s. I'm sure you've got similar experiences as well. I don't know that age or whether or not we could get them through a transplant is necessarily the right benchmark for who these patients are. I suspect that most patients, in fact, with myeloma would potentially be candidates. Because in general, even if they do get adverse events, such as cytokine release syndrome [CRS] or neurologic toxicity that has been demonstrated with, for instance, CD19-directed CAR T cells in ALL [acute lymphocytic leukemia] and diffuse large B cell lymphoma, the severity of those adverse events in myeloma patients getting a BCMA-directed CAR seems much less.

It doesn't mean that it doesn't happen. And it doesn't mean that it isn't scary to a patient when they get CRS. But in general, the severity seems much lower, at least a grade lower than what we see in CD19-directed CAR T cells. And it seems to be pretty easily managed with tocilizumab and/or corticosteroids for a majority of patients.

That's an important take-home message, that there aren't clear groups of patients for whom you would say, ‘No, you can't do this.’

I think the other piece, as we put that trial data and response in context, is to recognize what you just described, Noopur, which is that many patients have to be able to go through a process of apheresis, maybe with or without bridging therapy, and then wait 4 to 6 weeks for that product to be available. And that certainly does shrink the number of patients with triple-class refractory myeloma who may be able to wait, potentially, for a CAR T cell-directed therapy.

So while those response rates and depth of responses certainly are incredibly encouraging and are proof of principle that this strategy can be really effective, if you look at it on an intention-to-treat basis, the numbers might look a little different. Because, certainly, we know there are patients who have disease that just doesn't sit around and wait for the product to be made before it's ready.

I think there are a number of factors that go into it. And certainly, we have learned after the first and now the second CAR T cell was approved that there are patients who can wait that period of time. There are not necessarily physical limitations on who should or should

not be eligible for a CAR T cell. But I think understanding how it fits in the overall paradigm when you do have time to wait for the cells to be manufactured is another important point.

And for those just tuning in, you're listening to CME on ReachMD. I'm Dr. Sagar Lonial, and here with me today is Dr. Noopur Raje, and we're discussing CAR T-cell therapy and the new outlook it's providing for our patients with multiple myeloma.

Noopur, one of the adverse events that we do see is neurotoxicity. And it may differ between our 2 current FDA-approved products. You want to give us sort of a quick rundown of what that might look like?

Dr. Raje:
Both ide-cel and cilta-cel, we do see some acute neurotoxicity. We refer to that as ICANS. That's typically seen 3 or 4 days after you give that infusion. Fortunately for us, Sagar, with myeloma, we've seen very little in way of neurotoxicity, more so in the lymphoma and the leukemia population, and it is quite easily managed.

There is a small subset of patients specifically in the CARTITUDE trial wherein we saw some delayed neurotoxicity. And this happened anywhere between 30 days to about 100 days. And this was almost like a movement disorder, which was progressive. It happened in a minority of patients, and half of these patients did recover; the others unfortunately did not. One of the things which was talked through at the time was that this may be because patients who went in to get cilta-cel at that time had a very high disease burden, and that may have predisposed them to this delayed neurotoxicity.

So going forward, I think especially with cilta-cel, we try and tumor reduce patients so that we don't run into problems with this delayed neurotoxicity. And at least in some of the subsequent CARTITUDE trials, we have not yet seen this delayed neurotoxicity.

Sagar, I'm sure you've been asked by your referring physicians, as well as I have, when is it too early to refer a patient to CAR T cells? And I generally tell most folks is it's never too early. It's always a good idea to stay connected with a CAR T cell center because, as you just pointed out so nicely, there is this element of logistics which one needs to take into account. One needs to have a slot for the CAR T cells. And then one needs to plan the kind of therapy that they need to have before they can get to CAR T cells. So referring early is the way to think about CAR T cells so that you can get them through.

And I do think, given that we've seen such incredible results in kind of end-stage myeloma, moving this kind of therapy earlier on in the course of their disease is what is going to take place. We already, as you know, Sagar, we're doing clinical trials, even in the up-front setting. Those obviously are in the context of clinical trials, but we're doing it after 1 to 3 lines of relapse. And the earlier you do some of these CAR T cell treatments, the potential of this waiting and the potential of the need for bridging therapy, etc., will start hopefully going down.

In your experience, when you're using bridging therapies, did you have any specific therapies that you generally like avoiding, not so much after they've been leukapheresed, but before patients are actually leukapheresed for their CAR product?

Dr. Lonial:
Yeah, avoiding cyclophosphamide-based approaches. I think a lot of us end up using DCEP or VDT PACE in these patients at one point or another. And if you can avoid that kind of therapy, you might have a little bit more success. I think that's a whole nother avenue that we've not even begun to explore, which is how do you optimize the starting product, whether it's short course of an IMiD [immunomodulatory drug] or something, CELMoD [cereblon E3 ligase modulator], some treatment to try and wake up T cells, if you will, prior to collection. I think those are really exciting future concepts in how to make CARs better.

Dr. Raje:
Absolutely. We've talked a lot about the process of the CAR T cells. I think one really other important part is for patients to understand. Because in my experience, Sagar, and I'm sure it's the same where you're at, it is not just the patient but the caregivers and really communicating with the patients and their caregivers. It is a commitment. They have to stay close to the center for about 30 days; they are hospitalized for the first 10 to 12 days. And having that knowledge and understanding of what is required of them is critical for the success of CAR T cells.

Do you have thoughts on how we should be doing a better job at communicating with our patients as to what it entails?

Dr. Lonial:
You're absolutely right. The idea of trying to make sure they can anticipate what the adverse events might be. I've certainly had patients who did remarkably well and were young and fit and then developed some late events that required us to be a little bit more vigilant and perhaps even rehospitalize them for a short period of time. Making patients aware that just because you're day 15 or day 18 doesn't mean you're necessarily out of the woods for some additional late adverse events like macrophage activation syndrome or things along those lines, I think, is important from an expectation perspective.

Dr. Raje:
Yeah, it's been really exciting to see how patients are responding. We have patients who are out many, many months. And like you said, Sagar, I think we are still at the beginnings of understanding how best to optimize the use of CAR T cells for patients with myeloma. So I'm certainly very excited about this option of treatment for our patients. And as we begin to develop strategies to improve upon what we're already seeing, I can only imagine how incredibly useful this tool is going to be for our patients going forward.

Dr. Lonial:
Yeah, there are so many aspects of CAR T cell therapy. Noopur, what is your final take-home message for our audience?

Dr. Raje:
I think high response rates, Sagar, with this new technology and something which most of our patients should have access to, if not all, and with that, I hope that we can create very, very durable remissions in the majority of our patients.

Dr. Lonial:
You're absolutely correct. And for me, I think it's early access. As you mentioned, making sure that patients are sent into a tertiary referral center early in their disease course so that where a CAR T is going to fit can be adequately mapped out as opposed to the 11th hour when they have terrible counts or bad renal function, and at that time point the outcome and the ability to get there may be much more limited. So early access, I think, is the key.

I want to thank our audience for listening in and thank you, Dr. Noopur Raje, for joining me in this discussion today.

Dr. Raje:
Thanks so much, Sagar, for having me.

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