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

Real-World Experience With CAR T-cell Therapy in Late Relapsed Multiple Myeloma

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Dr. Cohen:
Hi, my name's Adam Cohen from University of Pennsylvania in Philadelphia. And it's my pleasure to be joined today by my colleague, Dr. Noopur Raje from Mass General Hospital in Boston. Hi, Noopur, how are you?

Dr. Raje:
Hi, Adam.

Dr. Cohen:
So, today we're going to be discussing our real-world experience using BCMA-directed CAR T-cells for patients with relapsed refractory myeloma. And so Noopur, I think I'll start with the first question. We obviously know in the trials these patients were really heavily pretreated, very refractory. In real life, which patients are you actually getting referred to you? And, when should our referring physicians be thinking about sending patients in for CAR T-cells?

Dr. Raje:
Yeah, I think this is a really important thing to think about and talk about, Adam, because as you know, as you pointed out, the clinical trials, they had to be heavily pretreated. Even if you go by the label right now, they've had to have at least four prior lines of treatment. In the real world, as you and I know, you know, we are using combination treatments upfront. I think most of us have switched to quadruplets, and even upfront, and we are using triplets at second relapse. So, by the time a patient comes to relapse number three, they've been pretty much exposed to both IMiDs, both proteasome inhibitors, and for sure, the CD38 monoclonal antibody. I always tell most of our referring community oncologists it's never too early to refer for CAR T-cells, because as you know, there's a lot of logistics involved in trying to get a patient through the whole process of CAR T-cells. But at least at the time of second relapse, I think people should start thinking about the referral and at least getting a sense of how to then try and put them on a list for the CAR T-cells and try and get them to the CAR T-cells in a timely fashion.

Dr. Cohen:
Yeah, and I completely agree. I think that the earlier, the better. And what I often tell them as well is don't wait till your patient is progressing on that fourth line of therapy. And then they come to us, and there's a long wait list basically, and we're scrambling to try to control their disease. And we're actually thinking of using this almost as a consolidation in some cases for patients who are responding to that fourth line treatment so that you can actually not have to worry about their disease escaping during manufacturing. So, I definitely agree with you there.

Dr. Raje:
Yeah, I think what you brought up about rapidly progressive disease is such an important thing. It takes four to six weeks for us to get

the CAR product back. And unless we start thinking about this process earlier, we're going to have those very refractory patients who we are not going to be able to salvage with these approaches.

Dr. Cohen:
Absolutely. And then another real-world problem is that we of course have two different products right now that are available to us. And so what do you guys do at your center? How are you determining which patients are getting which product?

Dr. Raje:
Yeah, that's a tough one, Adam. And I think all of us struggle with that. I think right now, you know, the demand is way more than what's available, and hopefully in the future that's not going to be the case. But as of right now, you know, we get what we can, and we have patients, we maintain a list and then we, depending on the needs of the patient, offer them either ide-cel or cilta-cel, depending on whichever is available. So, given that the demand is so much higher, I don't think it's so much of a choice right now. Going forward though, I do think this is going to be important for us to try and figure out. And you know, it's going to be important in terms of, if you just look at the efficacy data, they are obviously two-way different products. One has a very high response rate, and we are seeing at least at the two-year time point a progression-free survival which looks very reasonable. The other drug product, the, you know, the CR rates are a little bit lower, but even so the ones who achieved that stringent complete response do just as well. And their two-year PFS is pretty good. So, I, you know, over time once we get a better sense of long-term toxicities, of these two drug products, I think we will be able to better define who gets what. It could be dependent on disease burden, et cetera. As of right now, I don't think we have the data to speak to that. I don't know what you do at your center though. Do you have any specific, you know, criteria to one getting cilta-cel versus ida-cel, Adam?

Dr. Cohen:
At least right now, we don't. We're taking a very similar approach to you, in that there's far more patients who are waiting and need these products than we have slots. And so, we're really saying to patients, I'll discuss both with you, but whichever one you get, that's really the one we're going for. And some patients occasionally will want one over the other, but we try not to encourage that, and to really offer both. And again, as you know, these are both, you know, single-arm, relatively small, phase two studies. They weren't compared head-to-head. So, I think we have to be cautious and really sort of making firm conclusions about differences and efficacy. So right now, we're offering both. And I agree with you, as these start to move up a little bit earlier, perhaps we may start to pick and choose a little bit more which patients may be more suited for one versus the other. But I think we need a little bit more data in that regard.

Dr. Raje:
Yeah, that's going to be a tough thing to sort out once we, I mean, if, you know, I do think over time because these are so designer-specific and so patient-specific, you know, we are, of demand, is always going to be ahead of supply, what we are going to be able to supply. So, I think we just don't have enough drug products. So, the more we have the better it's going to be. And then over time, you know, given, I think this is something to learn from our lymphoma colleagues. We know that the three or four drug products approved in the lymphoma setting, and it's not as if they are all mutually exclusive, they're all targeting the same antigen. And yet in the lymphoma world, we have used one product after the other as well. If they have had a response, and this may be something we may end up doing for myeloma given time.

Dr. Cohen:
Absolutely. Another question that comes up in terms of which patients to refer in, or can we give this to patients who might have been excluded from the initial trials, like patients with renal failure, patients with CNS involvement, bad cytopenias, et cetera? So, what would you say to referring physicians who, you know, come to you with a question like that for a patient?

Dr. Raje:
Yeah, so, I think the fact that these drug products are approved, I do think we have to allow access to more patients. That's part of this whole approval process. We are very stringent when it comes to clinical trials. We do have to be careful though, and careful in terms of toxicity. So, you know, cytopenias is something we certainly allowed on the standard of care drug product, knowing that we are going to need more support and more close follow-up after they've had the CAR T-cell product. You don't want to take somebody with, you know, overt CNS disease, but that doesn't mean you don't refer, because part of the problem with myeloma, and I think you can completely appreciate this, Adam, you have a lot of medullary disease, so bony disease, very close to the CNS, and that confusion always comes up. Is this true CNS, because CNS disease in myeloma is exceedingly rare. And in those situations we've obviously allowed CAR T-cells. As far as renal failure is concerned, you know, we do consider it, we are doing studies as you know, you are doing them at your site as well, whether or not we can get away by getting rid of the fludarabine, for example, or can you do dialysis with fludarabine? Can you dose modify the lympho-depleting chemotherapy? But that's to me is still an open question. Do we have to use fludarabine, cytoxan in everybody? Or can we start begin, can we begin to do studies looking at alternatives specifically in patients with renal dysfunction?

Dr. Cohen:
Yeah, so I think I really agree with everything that you've said. That we don't have a lot of data, but that doesn't mean we should absolutely exclude these patients. And as long as you discuss the risk/benefits with them you certainly can go forward. And, and we've done the similar things in our center. We've treated patients with significant cytopenias, but we inform them of the risk of perhaps, you know, more transfusion need. And I like to have stem cell backup for those patients in some cases. And same with renal failure, we do the same thing. Well, we reduce or even eliminate fludarabine in some cases and have been able to successfully, you know, give CAR T-cells safely to patients. So, I wouldn't see that as a barrier to referral. At least, we should still have the conversation with the patient and potentially offer this to them if we still think it's in their best interest.

Dr. Raje:
No, absolutely. And which brings up the point, you know, every patient who has relapsed multiple myeloma should be referred. I think one of the things in the community is the thought process of this is not a transplant-eligible patient and therefore I will not refer for CAR T-cells. And what we've had to do, Adam, is a lot of education around that. You know, that with CAR T-cells, we've treated much older patients. We have treated patients with a lot of other comorbidities, and it's a very different patient population because you're treating with CAR T-cells at the time of active relapse. Whereas the transplant is generally being done when they're in a good remission. So, that has required a lot of education on our part. And I'm sure you've had to do the same with your, or, you know, referring physician base as well.

Dr. Cohen:
Absolutely, yep. But I do think that the word is getting out there that you don't necessarily have to be a high-dose melphalan candidate in order to, to get CAR T-cells. And, so I think we're gaining more experience with that little bit more frail population, too. All right, I think that's probably all the time that we have. So, I'd just like to thank you again for joining me in this discussion today.

Dr. Raje:
Thanks so much, Adam.

Announcer:
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