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

Mitigating and Managing Toxicities With CAR T-cell Therapy in Multiple Myeloma

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Dr. Raje:
Hello, my name is Noopur Raje, and I work at the MGH Cancer Center in Boston, and I'm thrilled to be joined by my colleague, Dr. Adam Cohen from the University of Pennsylvania. Welcome, Adam.

Dr. Cohen:
Hi Noopur, thanks for having me.

Dr. Raje:
So, what we're going to talk about Adam is toxicities associated with CAR T-cells and really strategies to try and mitigate some of these toxicities. And what I wanted to do was start out by talking about some of the acute toxicities first. We obviously have two very different CAR products. We have Ida cell and Cilta-cell, which work a little bit differently. Do you want to speak a little bit to what we see more acutely with one versus the other, and sort of the time frame of the acute toxicities that we manage?

Dr. Cohen:
Absolutely, so both of these products are associated with high rates of Cytokine Release Syndrome which is similar to other CAR products, and a somewhat lower rate of neurotoxicity. But the timing of onset can be different between the products. So, Ida cell is given at a higher dose. The median time to onset of CRS is typically within a day or so. Whereas Cilta-cell given at a lower dose, a little different product, median onset of CRS is around day seven. So, it's really important to know this when you think about, you know, when your patients are likely to get sick, and even how you could manage these patients. For instance, at our center we admit all our Ida cell patients right from the start of infusion, whereas Cilta-cell, if they're relatively stable, we'll give that as an outpatient and admit them on day five, and then plan to watch them during the, I guess, peak of CAR T, or CRS incidents.

Dr. Raje:
So, you know, CRS neurotoxicity are things that we manage in house most of the times, they are all hospitalized, but oftentimes I think, you know, it's hard to figure out the difference between CRS and neurotoxicity, and there's almost always that overlap. Somebody with a fever of 103 can certainly be a little confused, I would be. Is there, do you really need to differentiate between the two, and how do you manage your start with steroids? Do you do Tocilizumab or what, what's your strategy?

Dr. Cohen:
Right. So, you're certainly correct that there can be a little bit of confusion in the setting of high fevers from CRS, but, but you really do want to I think, differentiate these, if you can, and try to determine patients who have true ICANS, this Immune Effector Cell Neurotoxicity Syndrome. We do probably as you do in your center, the ICE score which is sort of this actual formal testing of patient's

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neurologic function, including their, you know, attention, and cognition, and handwriting, and if patients really do show deficits on there, it's important to intervene. And it's not just Tocilizumab, which is what we typically would give for CRS, but it's also steroids as well. And so, Dexamethasone is really, a very important treatment for patients who are developing this neurotoxicity. And importantly, it doesn't seem to impact the efficacy of the CAR T-cells if given for a short duration of therapy. And so, we are very generous with giving not just Toci, but also steroids, if someone's really developing true neurotoxicity in the acute setting.

Dr. Raje:
Yeah. I think what you highlighted is so important, Adam. Early on, when we started doing CAR T-cells, we were all worried about giving Dexamethasone, but actually mitigating these toxicities as quickly as possible is going to prevent them from getting worse, and there's data to show that it really doesn't impact the efficacy of the CAR T-cell product. Which brings up another rare toxicity, HLH-like, or the Macrophage Activating Syndrome. Again, with that, you want to treat early, but are there any other things that you would do for something like an HLH picture?

Dr. Cohen:
Right. So, I do think this is emerging, and fortunately, it's still fairly rare, at least in Myeloma. But we do see it. It can occur, sort of, contemporaneously, or shortly after CRS, or even some cases a little bit with later onset. And one of the key things is that, this may, this may respond better to es to the point of early referral for our patients Anakinra or IL-1 Blockade. And so that's really I think, something we've learned as a community, is if patients have gotten their Tocilizumab, they're defervescing, but that ferritin is really shooting up rapidly, their LFTs are really taking off, they're getting more Cytopenic; this is somebody you might be worried is developing a Macrophage Activation-like syndrome. And then adding Anakinra and or steroids on top of that may, maybe the way to prevent that from really getting worse.

Dr. Raje:
And this, again goes to the point of early referral for our patients. You know, you want disease burden, which is not really very very high because that then sets people up for all of these toxicities; CRS, neurotoxicity, HLH. So, if you will have a better controlled Myeloma, you're going to have better outcomes with the CAR T-cell strategy. But most of what we both talked about right now is something we do at the centers where CAR T-cells happens. I think it's really important for us to sort of highlight how some of our patients need to be followed, because as soon as they get discharged from the hospital they go back to the oncologist, or the hematologist who's been taking care of them. Are there specific things that you have folks beyond prophylactically, and what is it that you would suggest people look out for in terms of infection or blood counts, and so on and so forth?

Dr. Cohen:
Absolutely. Now this is really an important point to make. And so, in terms of blood counts, I'll mention we sometimes see this bimodal-almost Cytopenias where they'll become cytopenic from their Fludarabine Cytoxan, they'll recover, and then they may have a second dip, and actually have a later cytopenias. Then this may be from CAR T-cell mediated inflammation in the marrow, and that can sometimes be persistent even to a few months. And so it's really important to monitor these patients, to provide growth factor and transfusion support. There's no reason you can't give GCSF once they're passed the acute, you know, CRS phase and, and acute inflammation. So that's one key point. And then you mentioned prophylaxis, and I think this is another one. We're really learning infection is a major issue in these late-line Myeloma patients with these BCMA targeted therapies. So, at our center, we typically give a Quinolone and Azole, like Fluconazole, during the initial nadir period. We also start Acyclovir, or something equivalent for shingles, as well as Bactrim for PCP prophylaxis. And that is continued actually for a prolonged period, usually several months. And I actually follow CD4 counts. I'm not sure if that's something you do at your center, but, I've been impressed by how long these patients can have a CD4 lymphopenia and significant immune deficits even three to six months post-CAR T-cells.

Dr. Raje:
Yeah, no, we, you know, we don't traditionally look at CD4 counts except on clinical trials. But the one thing to add there is, given that we are using all BCMA directed strategies, we are using IBIG in patients once their immunoglobulin falls below 400, we are certainly using PJP prophylaxis as you are, and patients are on Acyclovir. We haven't used a lot of Fluconazole, Adam. We haven't seen a lot of fungal infection. Yes, Fluconazole in the immediate, you know, the acute toxicity from Fludarabine when they're hospitalized, maybe, if they're spiking fevers, but not outside of that. One, you know, you mentioned this earlier, you talked about outpatient CARs. We haven't done it as yet in Myeloma, at least at MGH, but you seem to have done it with Cilta-cell. And what is the patient profile like for you to be comfortable doing outpatient CARs?

Dr. Cohen:
Yeah, so certainly a very reliable patient. Somebody who we know is going to be staying very nearby our center and is able to come back in for almost daily evaluations and counts for that, for that first week. And also, somebody with relatively low tumor burden. I mean,

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I think that's where we feel more comfortable that they're unlikely to have an early, you know, CRS or, or some sort of early complication. So, it is an individualized decision. We're not doing it with everybody. somebody with very rapidly growing disease, a lot of extramedullary disease, I wouldn't do it. But somebody who's in a pretty good response on bridging therapy, I'd feel more comfortable.

Dr. Raje:
Yeah. As, as we are moving these products earlier on in the course of treatment, do you think we are going to be able to do more of these as an outpatient, given that their disease burden is going to be lower, and they're going to be hopefully fitter than what we've done thus far?

Dr. Cohen:
Yeah. I, I really hope so. And, and, you know, fortunately, we've had experience with this on several of our own in-house trials. So, we have to have the, I guess the setup for it, that, the logistics where you can get patients in quickly and your emergency room docs know what to do et cetera, but I think it can be done. And particularly because the CRS is later with Cilta-cell that's a product where I think it can certainly be explored.

Dr. Raje:
Any words on sort of delayed neurotoxicity at all, Adam? Should we be monitoring? Should we be looking out for it in some ways?

Dr. Cohen:
Yeah. I think that's a great point because this can occur even after patients have, have left the hospital, have gone back to the community. And so what was described is really a Parkinsonian-like events that were seen in the Cilta-cell study. It's been described with other CAR products as well. And it can be as subtle as a personality change or loss of sense of humor. That's how one of my patients was first described by their spouse. They can have handwriting changes, they can have difficulty with, sort of, fine motor movements. And so, yes, I think it is important to keep an eye out for this. The patients who got this seemed to be those that had very high tumor burden going into their CARs, they had typically high-grade ICANS or CRS previously, and very high levels of CAR T-cells. You know, you could see very high lymphocyte counts persisting out. So, if you see any of that in those, if you have a patient like that, then you really need to be on the watch for it.

Dr. Raje:
And follow them more carefully. You know, I agree with pretty much everything you said. Having said, you know, we've spent the section talking about toxicities. I did want to highlight the fact that in general CAR T-cells in Myeloma extremely well tolerated. And we are just, you know, recommending all of these to be on the lookout for. Thanks so much for talking through toxicities, Adam. I hope our listeners enjoyed this episode. Thank you.

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