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Monitoring Adverse Events Post-CAR T: The Latest Approaches and Best Practices

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Bristol Myers Squibb. This is a non-certified educational series produced and controlled by ReachMD. Here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to the *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and joining me to share key strategies for monitoring adverse events after CAR T-cell therapy is Dr. Evandro Bezerra, who's a hematologist-oncologist and Clinical Assistant Professor at Ohio State University Comprehensive Cancer Center in Columbus. Dr. Bezerra, thanks for being here today.

Dr. Bezerra:
Thank you for the invite. It's a pleasure to be here.

Dr. Turck:
Well, starting with a bit of an overview, Dr. Bezerra, would you tell us how the scope of post-CAR T monitoring has changed over the past few years?

Dr. Bezerra:
That's a very important question because it's changed a lot. From the beginning of CAR T-cells—back when they were in a clinical trial and since the initial approvals in 2017—the monitoring of post-CAR T was heavily done in patients because of the management of the main acute toxicities: cytokine release syndrome and neurologic toxicity, now known as ICANS. But now, with better strategies to identify patients at high risk of developing these toxicities and better strategies to manage these toxicities, there is a significant shift nowadays to minimize the inpatient time and start to move to have these products delivered in the outpatient fashion. And of course, with very close follow-up—patients being seen at least daily—any clinical change would be reported in a short amount of time to the hospital to be managed. On top of this, the shift from the initial prolonged inpatient monitoring post CAR T to now moving towards an outpatient monitoring post-CAR T is very important for both patient's quality of life experience and also for healthcare resource utilization, improving the access for this important therapy.

Previously, we used to keep patients close to the CAR T center for the first month post-CAR T. A recent publication led by the Kansas University Group showed that most of these acute toxicities post-CAR T happen in the first 2 weeks at onset. And now recently, the FDA changed their requirements for CAR T, allowing the patients after their first 2 weeks to not necessarily be close to the CAR T center for the whole first month.

Dr. Turck:
Now, cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, or CRS and ICANS, remain the two most recognized toxicities of CAR T therapy. But even within the acute window of early stage management, are there areas of post infusion care that still need refining?

Dr. Bezerra:
Yes, that's a very important point because the main concerns with CAR T-cell have been CRS and ICANS in the acute setting. But a recent publication has shown that the main driver of non-relapsed mortality in patients getting CAR T is actually infection.

Another important toxicity in the acute setting that we need to pay attention to is the post-CAR T cytopenias, the ICAHT. These patients

can have significant cytopenias. For example, the neutropenia can increase the risk of infection but also the transfusion needs for red blood cells and platelets as well as bleeding risk. We have some emerging data and guidelines trying to risk stratify patients that have a higher or lower risk of hematologic toxicity post-CAR T based on baseline counts, disease burden, and prior therapies to try guide us on how intense the monitoring should be.

And one last comment as we still see this complication and it can be quite challenging to manage: HLH post CAR T. It is a spectrum. Sometimes it's very hard to differentiate what is just a post-CAR T cytopenia or inflammatory syndrome versus HLH. As you know, some of these markers are not specific, and none of these markers are very highly specific for HLH, and this is something that is very challenging in the clinical practice: when to make the call that a patient has HLH and pull the trigger for very aggressive measures in terms of immunosuppression. Controlling the inflammatory side effect can increase significantly the risk of infection.

Dr. Turck:
And since we're very fortunately seeing more patients live months and even years after CAR T infusion, for what long-term adverse events should we be on the lookout?

Dr. Bezerra:
That's a very important question because CAR T is a breakthrough therapy that allows patients that do not have other treatment options to now have long term remissions of heavily pretreated, relapsed/refractory hematological malignancies. Despite the long-term remission, they still are at higher risk of non-relapsed mortality, and this risk is mainly driven by infection. Infection risk comes from multiple reasons. One of them, importantly, is these patients frequently develop hypogammaglobulinemia. So that's one thing that needs to be very carefully monitored, like the IgG levels to see if the patient has the need for IV Ig infusions, especially if the patient has recurrent or major infections. Another important reason is the patients may frequently have T-cell inferior velocity counts so the patients need to be on extended prophylaxis for infection for acyclovir, PJP prophylaxis, and CD4 count monitoring, too. And another reason that increases the risk of infection, like I mentioned earlier, is the post-CAR T hematotoxicity. Patients can become neutropenic, and if they do, they need to be on neutropenic prophylaxis.

Another important cause of non-relapsed mortality in long-term survivors from CAR T that are in remission is second malignancy. The relationship between CAR T and the second malignancy isn't clear, and this doesn't change the benefit/risk ratio of CAR T because CAR T allows these patients to be in long-term remission. So one important thing to keep an eye on in patients that have cytopenias and have a low threshold is to investigate the bone marrow to make sure that this is not just a CAR T-cell effect and that the patient is not evolving with a therapy-related myeloid malignancy.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Evandro Bezerra about the best ways we can monitor adverse events after CAR T-cell therapy.

Now, as I understand it, Dr. Bezerra, there's a need for flexibility in monitoring protocols. So how do we individualize post-CAR T follow-up based on patient risk factors or treatment history?

Dr. Bezerra:
I think I mentioned earlier that one of the main complications—not just in the acute setting, but also after the acute phase of post-CAR T—is the myelotoxicity, the hematologic toxicity, and the low blood counts. And we do have a score published by Dr. Kai Rojeski. She tried to risk stratify the patients with a higher or lower risk of developing hematologic toxicity. And based on this score, you can decide how close you're going to monitor the counts after that acute phase. On top of the baseline counts and baseline features in the previous bone marrow testing, you can see inside of the myeloid disorder. Also, since these are heavily pretreated patients, patients who have a high disease burden pre-CAR T are going to be at higher risk of having hematologic toxicity post-CAR T, so they may need a closer follow-up with blood counts. And also, after the CAR T and after that acute phase, know where the counts are to know how closely they should be monitored.

Another factor that's important to this individualization is the patients' prior therapies. Have they already had a lot of B-cell depleting therapies, like rituximab, and did they already have low IgG levels at baseline before CAR T? It can be very hard for the IgG levels to recover after CAR T in a short term, so this patient is going to need to at least have IgG levels monitored carefully and also probably be on IVIG too.

Dr. Turck:
Now, looking at technology's role in this space, would you walk us through how telehealth, remote monitoring, and even mobile labs are shaping how we provide long-term care for patients who receive CAR T-cell therapy?

Dr. Bezerra:
So I think that telehealth may allow patients that live far from CAR T centers to at least have a discussion with CAR T doctors about what's CAR T, the benefits, and the risks because this type of discussion might be very hard to be dealt by physicians that are not used to handling patients receiving CAR T-cell. So telehealth visits as a first point of contact could allow the patient to have this initial education about the benefits and risks of CAR T so that they can make a decision about going closer to a CAR T center to further consider their therapy.

Another important point is the use of wearables that can track the vital signs when patients are being managed in an outpatient setting post CAR T; we can detect early signs of change in vital signs that can require the patient to come back to the CAR T center to be evaluated.

Dr. Turck:
Before we close, Dr. Bezerra, let's look ahead for just a moment. Could you tell us anything about upcoming emerging guidelines or consensus statements on the horizon that we should be aware of?

Dr. Bezerra:
There is a lot of discussion in the transplant cell therapy society, hematology society, and oncologist society about both America and Europe putting together a guideline to have more uniform recommendations about how to follow up these patients post-CAR T. I think we already have solid guidance for the acute phase for post-CAR T. We have some ideas based on a lot of review papers and also some publications. But we don't have a formal guideline unifying how to follow up these patients for all the different spectrum of complications these patients may have. We do have a lot of good guidelines for infections, specifically, and now some for counts issues and secondary malignancies. But I think the societies are still working to sit together and unify some guidelines to layout the follow-up plan these patients should receive and also interventions to prevent complications.

Dr. Turck:
Well, as those reflections bring us to the end of today's program, I want to thank my guest, Dr. Evandro Bezerra, for joining me to share these key strategies for monitoring adverse events after CAR T-cell therapy Dr. Bezerra, it was great having you on the program.

Dr. Bezerra:
Thank you. It's my pleasure.

Announcer:
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