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

Preventing Adverse Events in CAR T-Cell Therapy: The Evolution of Safety Protocols

Announcer
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Dr. Turck:
This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Here with me today to discuss the evolution of safety protocols for CAR T-cell therapy is Dr. Tara Graff. Dr. Graff is a medical oncologist who leads a community-based clinical trial program at Mission Cancer and Blood in Des Moines, Iowa. Dr. Graff, welcome to the program.

Dr. Graff:
Thank you for having me.

Dr. Turck:
Well, to start us off, Dr. Graff, we know there were safety challenges early on with CAR T-cell therapy. What can you tell us about the nature of those challenges and what you presently see in practice?

Dr. Graff:
So, CAR-T was a novel therapy, right? Something we haven't seen before: different side effect profiles with something called CRS, or cytokine release syndrome, and something called ICANs, which is basically a neurotoxicity syndrome. And so these were adverse events that we were not used to seeing with conventional chemotherapy, immunotherapy, or even transplant in our lymphomas.

So with that, there's always a learning curve, and initially, when we first started doing CAR T-cell therapy, especially on the clinical trials, there were a lot of events within the CRS and neurotoxicity components. And so with that, the treatments initially were felt to be more toxic because these patients were experiencing high rates or high grades of these events.

So with anything, we needed to figure out a way to mitigate those and lower those risks for future trials now that these products are commercially approved.

Dr. Turck:
Now, how have these safety protocols for CAR T-cell therapy evolved over time, and what's our current approach?

Dr. Graff:
So within the trials, there were real-world cohorts that were developed to look at different interventions, so the earlier use of corticosteroids. Initially, it was felt that if we use steroids too soon or prophylactically to decrease the rates of CRS, that somehow, we may affect the CAR T efficacy or the way that the T-cells would expand. And we were able to show that that does not seem to be the case.

So there were additional cohorts that were added to the initial trial, and one trial in particular called ZUMA-1 looked at a specific cohort—cohort number four—with the earlier use of corticosteroids as well as tocilizumab, which is a medication that's used to break the CRS cycle. And by doing those earlier interventions, these patients actually had fewer events of CRS.

And in terms of grade or the severity of those events, those were much lower as well, showing that with time, it's a learning process, right? You never do it perfectly the first time, and you don't do it perfectly even later, but you learn over time. You learn what can be done to make therapies safer while maintaining efficacy.

And that's what's evolved over the last several years: we know how effective CAR T is, and it was just figuring out with time and a little finesse how we could take those risks of CRS and neurotoxicity and lower them with earlier intervention strategies.

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. Tara Graff about how safety protocols for CAR T-cell therapy have evolved in recent years.

So given that evolution, Dr. Graff, when the rubber meets the road, what strategies can we use to implement the current safety protocols into practice?

Dr. Graff:
So, I think just having a universal protocol. I know a lot of centers and sites do things a little bit differently, but what we've all learned over the last few years is that having those such protocols in place—aggressive hydration, prophylactic use of corticosteroids, the early intervention strategies of using tocilizumab and not "waiting it out"—I think those are the things that are really, really important. I think most centers across the country have adopted that.

Now, there's different CAR T products out there, right? We use them in non-Hodgkin's lymphoma and myeloma, and there are some nuances. But knowing in your heart of hearts that it's okay to intervene on these patients and break this cycle of CRS earlier rather than later is really changing how patients tolerate these products, and you have a better overall understanding of how the T-cell product works when you do have these earlier intervention strategies.

Dr. Turck:
And looking at a slightly different facet of this, would you tell us about the roles of multidisciplinary collaboration and continuous monitoring?

Dr. Graff:
I like this question because a lot of our patients start out in the community, right? Not all patients are able to have a CAR T product infused where they live, so I include the multidisciplinary approach—not only including the team that's present in the hospital where the patient might be getting the CAR product, but also in the community.

So for me, I'm part of that team along with the physician who I work with very closely who does the CAR T-cell therapy as well as the nurses that are on site in clinic with me. Communication is really key. Obviously, what's going on at the center when things are happening is very, very important. But then there's also a lot of communication and pieces that are needed in the referral pattern to CAR T. And then, once the patient has had a CAR T product infused and made it through that highest-risk period, those patients then have to return to their primary oncologist in many settings.

And so, what does that look like? You need to be able to have a very clean hand-off and really a relationship with the CAR T center for a long time to come because that patient is basically yours. You're sharing now, right? It's a shared management. So I look at this as a true multidisciplinary approach, not just with one physician heading it up, but really, the primary oncologist, the CAR T-cell physician, nurses on both sides, and clinical care coordinator—that really kind of is the glue in the middle. So I think all those pieces have to be in place to keep the best safety practices in mind for the patient.

Dr. Turck:
And before we close, Dr. Graff, from a high-level view, do you have any final thoughts on contemporary safety protocols for CAR T-cell therapy?

Dr. Graff:
You know, CAR T has changed a lot over the last six years, maybe when the first trials were being done. And I could be wrong because time goes by even faster than that, but we've come far in our products to the point that some products are being administered outpatient. Patients don't even have to be inside the hospital or on the CAR T unit to receive these products.

So by implementing these different safety strategies or intervention strategies, as we've been talking about, with the fluids, earlier use of corticosteroids, and quicker intervention with tocilizumab to break the CRS cycle, we're allowing patients to even receive these products on outpatient basis.

So again, with the knowledge that comes over time, practice makes perfect, right? And I don't want to use the word perfect in anything, but essentially, the more we do something, the more we learn. And now we're able to take these therapies that once were very high acuity inpatient strategy and even bring them over to the outpatient side in some situations—even to the point that some patients are able to return home, back to their own beds, quicker than they initially were.

So again, it takes time to understand the intricacies of these new novel therapies that we're using and the ways that we can make them safer for our patients. And at the end of the day, that's all that matters for these patients and getting them back in their own beds.

Dr. Turck:
Well, as that brings us to the end of today's program, I want to thank my guest, Dr. Tara Graff, for joining me to share her insights on safety protocols for CAR T-cell therapy. Dr. Graff, it was great having you on the program.

Dr. Graff:
Yes. Thank you for letting me join.

Announcer
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