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

Enhancing Outcomes in Relapsed/Refractory B-ALL with CAR T-Cell Therapy

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Kite Pharma. Here's your host, Dr. Gates Colbert.

Dr. Colbert:
This is *Project Oncology* on ReachMD, and I'm Dr. Gates Colbert. Joining me to discuss CAR T-cell therapy for patients with relapsed/refractory B-cell acute lymphoblastic leukemia, or B-ALL for short, is Dr. Ryan Cassaday, who's an Associate Professor in the Division of Hematology-Oncology at the University of Washington School of Medicine in Seattle and the Associate Professor in Clinical Research Division Fred Hutchison Cancer Center. Dr. Cassaday, welcome to the program.

Dr. Cassaday:
Thanks a lot for having me, Dr. Colbert.

Dr. Colbert:
So if we start by examining the latest long-term data, Dr. Cassaday, how has CAR T-cell therapy impacted overall survival rates for patients with relapsed/refractory B-ALL?

Dr. Cassaday:
So we now have two products that have multiple years of follow-up from pivotal studies that led to their respective approval. There's tisagenlecleucel, which was approved several years ago now in children and young adults with relapsed/refractory B-cell ALL. The study that led to that approval was the ELIANA study, which I may occasionally refer to. And then the other product is brexucabtagene autoleucel, or brexu-cel. The study that got that product approved about a year-and-a-half ago now was called ZUMA-3. As we get farther and farther out, there appears to be a bit of a plateau on the relapse or event-free survival curves at about 40 to 50 percent with these products. So in other words, for patients with relapsed/refractory B-ALL who receive these different approved CAR T-cell therapies, there's about a 50ish percent chance of being alive and in remission several years later.

Now while that obviously leaves a lot of room for improvement, it's important to remember that before we had some of these newer agents for B-ALL, virtually everybody with relapsed disease would die within a year or two. So to have even approximately half of patients alive years later is truly an astounding improvement in terms of the options that are available.

Dr. Colbert:
And how about durable remissions? What does the long-term data say about CAR T-cell therapy's impact on that?

Dr. Cassaday:
When you look at overall survival of 3 years of about 40 or 50 percent, you can feel fairly confident that that subgroup of patients are the people who experienced durable remission from the CAR T-cell therapy. In other words, if they got CAR T-cells and it didn't work or it worked only transiently and their disease came back, unfortunately, they're probably in that other half of the subgroup that ultimately died.

So there are a few kind of nuances that have started to emerge; this is by no means a settled topic, but I would say from some of the things that have started to come out from these different long-term follow-up and collaborative projects from real-world evidence, there are a few sort of hints that point toward who we might be able to identify as more or less likely to experience durable remission. So for example, a real-world experience with the brexu-cel product in adults, patients who received some form of treatment after a response to

CAR T-cell therapy—whether that was a stem cell transplant or a targeted tyrosine kinase inhibitor for pH-positive ALL—those patients tended to do better and stay in remission longer. There's some biases in that, of course, but there does appear to maybe be a signal of that. But again, that's by no means a settled topic. There's a lot of interest in trying to understand other biomarkers like persistence of CAR T-cells, surrogates of CAR T activity like B-cell aplasia, and hypogammaglobulinemia, things of this nature. So there's a lot that's still trying to be understood in terms of trying to identify the patients that are most likely to have lengthy responses to CAR T therapy. But suffice it to say, from what we can see, if you can make it a year or two without having a relapse after an initial response, there's a pretty good chance that the disease is going to stay away.

Dr. Colbert:
And with that data in mind, are there any factors that seem to affect these long-term outcomes?

Dr. Cassaday:
So there are some factors that are maybe predictive of long-term response that clinicians can identify or recognize up front so that you know before going into CAR T-cell therapy if a patient in front of you is maybe more or less likely to experience that outcome. So maybe the one that's most practical or applicable is disease burden. So in patients that have a relatively low disease burden when they are receiving their CAR T-cell therapy, there tends to be a better chance of not only response but durability of response.

Another kind of similar idea is exposure to other therapies before receiving CAR T-cell therapy. The ones that are most applicable in this patient population are the CD3/CD19 bispecific T-cell engager, or BiTE, blinatumomab, and then the CD22 targeted antibody drug conjugate inotuzumab ozogamicin. So blinatumomab and inotuzumab ozogamicin are the other products that are approved for relapsed/refractory B-cell ALL.

Dr. Colbert:
For those just joining us, this is *Project Oncology* on ReachMD. I'm Dr. Gates Colbert, and I'm speaking with Dr. Ryan Cassaday about using CAR T therapy to treat patients with relapsed/refractory B-cell acute lymphoblastic leukemia.

Dr. Colbert:
So, Dr. Cassaday, now that we know about how CAR T-cell therapy can impact patients with relapsed/refractory BALL, can you tell us who's an appropriate candidate for this approach?

Dr. Cassaday:
While medical comorbidities certainly have to be considered because of some of the toxicities of these products, there are relatively few, in my opinion, that represent an absolute contraindication. In reality, there were relatively strict eligibility criteria for the clinical trials that got these products approved, which ultimately means we don't have as much experience giving CAR T-cell products to patients with severe kidney disease, severe neurologic issues or complications, cardiovascular disease, and so forth. So for any patient with some of these medical issues, there would need to be a strong amount of caution about recommending CAR T-cell therapy to them because of what could end up being pretty severe cases of either cytokine release syndrome or immune effector cell-associated neurologic syndrome, or what we call ICANS now, neurologic toxicity. Or just worsening of their underlying medical conditions that these different complications could potentially precipitate.

On the other hand, there are really some important psychosocial factors that have to be considered with this product. It's not as complicated as referring somebody for allogeneic stem cell transplantation, in part, because the risks of really long-term, chronic debilitating conditions like GVHD and so forth are really not applicable to CAR T-cell therapy. It still requires a significant amount of social support. Patients generally have to be able to get to the center that can offer CAR T-cell therapy. So if they live in a relatively remote area or live outside of a big city and they have to live within about 30 minutes of the clinic that offers the product, that, by itself, could be a huge barrier. Patients often are required to have a caregiver, somebody that can be with them when they're not in the hospital. So if it's somebody who lives alone or someone who is estranged from their family or doesn't really have many close contacts, that can also be a significant barrier.

Dr. Colbert:
And once the patient begins treatment, what adverse events might they experience and how do you manage them?

Dr. Cassaday:
There's really a couple phases I would say of the toxicity profile with these products. The early toxicities are what really got a lot of the attention early on as these products became available, and those are cytokine release syndrome, or CRS, and the neurologic complications that can arise. And the names for this have gone through a few different forms, but the current nomenclature used by most is the rather cumbersome acronym ICANS for immune effector cell-associated neurologic syndrome.

So in general, CRS is typically managed with supportive care, antipyretics, IV fluids, and anticytokine therapy, generally, tocilizumab. There are certainly active areas of investigation to try to recognize or identify other interventions or CRS, but currently the only real specific therapeutic that's available is tocilizumab. ICANS remains more of a mystery in terms of the optimal way of managing it. Treatment currently relies mostly around corticosteroids, usually dexamethasone, and for more severe cases, high-dose methylprednisolone is often used; this is like the gram of methylpred daily for a few days kind of dosing. Beyond that, we don't really have a great deal of understanding of how to treat that when it happens. It's mostly hope that the patient doesn't get it.

Once you get about 2 or 3 weeks out from the cell infusion, the likelihood of developing those complications is vanishingly small. Patients may still be experiencing some of the sequelae of them or the complications of the treatments for them, so unfortunately, all these different interventions are immunosuppressive by themselves, so infections can sometimes become more of a problem, particularly in the small number of weeks after CAR T therapy. So that becomes a problem and it's mostly opportunistic infections that you might expect from high-dose corticosteroids, so viral infections, fungal infections, things of this nature.

Once you get into the months out from CAR T-cell therapy, the side effect that is probably the most notable or challenging is hematologic toxicity, so prolonged cytopenias. These can sometimes just be a nuisance where patients just don't quite understand why their platelet count is 60 if they're in the remission and they're not getting chemo anymore. But it's not affecting their day-to-day life. But there are also patients that have profound pancytopenia that are on growth factors and broad-spectrum antimicrobials that are coming in for transfusions frequently that are getting stem cell factors and romiplostim and eltrombopag, and all these different things that people have studied—none of which clearly are effective, certainly not approved in these settings—so there's lots that we don't know about this complication. It is correlated with the severity of CRS that patients experience, so if people have a pretty complicated course early on, they're more likely to experience these things.

Dr. Colbert:
And lastly, Dr. Cassaday, putting all this together, how is CAR T therapy changing the relapsed/refractory BALL treatment landscape from your vantage point?

Dr. Cassaday:
So to have CAR T-cell therapy available for this patient population has provided a really important new option. It is important to recognize that it is not the only option for these patients, that we do have other therapies available that weren't available 5 or 10 years ago. inotuzumab ozogamicin, blinatumomab, those therapies still represent important advances as well. So it's not that everybody needs to get CAR T-cells as soon as humanly possible. But what it does provide is a really important option that we've only really kind of scratched the surface in terms of understanding where this therapy could potentially be used.

Dr. Colbert:
And that's a great way to end our program today. And I'd like to thank my guest, Dr. Ryan Cassaday, for joining me to discuss how CAR T-cell therapy can impact patients with relapsed/refractory B-cell acute lymphoblastic leukemia. Dr. Cassaday, it was great speaking with you today.

Dr. Cassaday:
Thank you, Dr. Colbert. Thanks a lot.

Announcer:
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