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CAR T-Cell Therapy for Relapsed/Refractory B-ALL: Evaluating Real-World Data

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

Dr. Turck:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and joining me to dig through some key data on CAR T-cell therapy for relapsed/refractory B-cell acute lymphoblastic leukemia, or B-ALL for short, is Dr. Gregory Roloff, who's an Assistant Professor of Medicine at the University of Chicago. Dr. Roloff, thanks for being here today.

Dr. Roloff:
It's a pleasure to be with you, Dr. Turck. Thank you for having me.

Dr. Turck:
So to get us started, Dr. Roloff, what does the real-world evidence from various countries tell us about the efficacy of CAR T-cell therapy for relapsed/refractory B-cell ALL?

Dr. Roloff:
Well, it's a good question. And thankfully and encouragingly, I think the data are starting to pan out and tell us that the response rates for CAR T-cell therapy, at least in adults with relapsed/refractory B-ALL, are quite high. Most of the reason that I get asked these days to talk about CAR T-cells in B-ALL is because I have the privilege of co-leading a large real-world data-sharing consortium alongside Lori Muffly at Stanford, and we have been working for about—it's gone by very fast—the past 2.5 years now to create a network of centers to engage in data sharing for CAR T-cell therapy, and specifically for a particular CAR T-cell product called brexu-cel, or brexucabtagene autoleucel, for adult patients with relapsed/refractory B-ALL.

The two big questions that we were trying to get at here was about the real-world response rate. And then we'll talk in a few minutes about some safety and toxicity data. And at least in our cohort of 189 patients who had a median follow-up of about 11.5 months, we observed very high response rates retrospectively, of course, of about 90 percent, which is high. And we all know that there's caveats about comparing cross trial and using real-world data versus trial data and versus other real-world data. But we recognize those caveats, but at least with rare indications and rare diseases, we all like to have some sense of as to how our numbers compare to other data that's out there. And so we have an understanding that at least amongst our 90 percent CR that we're seeing retrospectively, about 80 percent of those are MRD-, or measurable residual disease, negative CRs, which mean they're of deep quality. And from some international data that has just been published and was presented also within the past year at the major meetings of centers in France, our data are relatively similar to theirs. They saw a response rate in the mid to high 70s and about another 80 percent MRD-negative response rate.

Dr. Turck:
And how about CAR T safety in B-ALL? What does the real-world evidence show there?

Dr. Roloff:
It's an evolving story. So when we talk about safety in B-ALL and CAR T-cells with B-ALL, there's really two main characters. The first toxicity is what we call CRS, or cytokine release syndrome, which to be perfectly honest with you, it resembles sepsis. It's when patients get hypotensive and are spiking fevers and look ill, to put it quite simply. Oftentimes, the higher grades will require ICU-level care with medicines or vasopressors to increase the blood pressure and lots of intensive supporting monitoring.

And the other character in the story of toxicity we call ICANS, or I like to just call it neurotoxicity for short. It's immune effector cell-associated neurotoxicity syndrome. So we'll just stick with neurotoxicity. And it's just what it sounds like. And oftentimes it will manifest with delayed or word-finding difficulties, with trouble speaking, and can progress all the way to non-responsiveness in coma.

And what we see, at least in the ROCCA real-world data, is that while most patients will experience CRS, it's a relatively low number of individuals who experience high-grade CRS, but kind of the opposite is true for neurotoxicity. We observed about a 30 percent rate of high-grade neurotoxicity in patients treated with brexu-cel as a standard therapy. Most of the time, though, these patients are able to be identified early and receive therapies that will allow them to have some kind of turnaround. We did not see a significant number of deaths from neurotoxicity alone of patients who are otherwise in remission. And most of the deaths in this cohort that we saw were due to relapsed and refractory disease and progression and complications from bone marrow failure.

Dr. Turck:
Now turning our attention to the long-term follow-up data that we have at our disposal, what do we know about durability of response and the potential for extended survival benefits?

Dr. Roloff:
I think that's probably the million-dollar question here because we've at least been able to confirm what many of us have been observing anecdotally, is that it seems like we see a large number of responses in patients treated with CAR T-cell therapy for ALL, and the question is, how do you keep them there? And practice patterns vary by doctor and by center, and even doctors within centers who may do things differently. And so you can ask yourself, well, what does the long-term data tell us about individuals who were just infused with a CAR T-cell product as a destination therapy? And the trouble is we don't have incredible long-term follow-up yet. There was a longer-term follow-up paper from the group who did the trial of brexu-cel that ultimately got it approved and had about 3 years of follow-up, but relatively few of those patients went on to other consolidative therapies like stem cell transplant. But we're seeing kind of a flattening of the curve, or long-term progression-free survival, and the absence of other consolidative therapies around the 35 to 40 percent mark. And so if those data read out and longer follow-up are able to confirm the observations we made, this is pretty commensurate with what we see in lymphoma patients of about a 30 to 40 percent long-term progression-free survival in the absence of other therapies that could potentially serve as a, I almost hesitate to use the C-word, but essentially as a cure for some of those patients. But the problem is that means that the majority don't get there.

Dr. Turck:
For those just joining us, this is *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Gregory Roloff about the real-world data and long-term evidence supporting the safety and efficacy of CAR T-cell therapy for patients with relapsed/refractory B-cell acute lymphoblastic leukemia, or B-ALL.

Now speaking of long-term follow-up, Dr. Roloff, what challenges do clinicians face when monitoring their patients who are being treated with CAR T?

Dr. Roloff:
One of the more interesting modalities that has come to our toolbox in recent years refers to not just measurable residual disease monitoring, but a specific type of MRD monitoring through next-generation sequencing. The other options, of course, for MRD monitoring are via flow cytometry or PCR. But I think that this next-generation sequencing-based modality is probably the most popular as of now, and it’s probably going to be growing in terms of its capture of the market, if you will.

And one of the things that we've been able to observe is that even for patients in a morphologic complete remission, their outcomes stratify very strongly according to their NGS-based MRD status. And I would say it’s probably safe to assume that individuals who have an NGS/MRD positivity but otherwise are in morphologic CR will go on to behave more like patients who have frank disease as opposed to those who are in a deep MRD-negative remission. And one of the takeaways from our data would be that as soon as NGS-based MRD starts to pop positive, you need to think about an impending relapse and perhaps mobilize some type of therapy for relapse prevention, whether that is starting immune-based therapy, getting a TKI going, or planning an allogeneic transplant; it's going to vary patient to patient. But this tool allows us some type of lead time to see what's coming, and it tends to have highly predictive abilities. And so I think the power of these technologies will continue to grow and aid in our clinical decision-making.

Dr. Turck:
And would you paint a picture for us of why else it's so important that we continuously monitor our patients?

Dr. Roloff:
Sure. So as patients have their first assessment after a CAR T-cell infusion—it typically happens around day 28 or day 30—they'll get a bone marrow biopsy, and depending on center-to-center dynamics, they'll have some type of MRD assay sent. And by doing that and

doing it in a longitudinal fashion—it's hard to interpret data if you just have one datapoint, but data is much more important if you can build trends and tell a story over time. And so if you're able to get a baseline and follow longitudinally, you'll be able to track even minuscule amounts of disease. We're talking one clonal cell in the background of a million normal cells. And by being able to capture a trend, you'll be empowered by the data to be able, if it were, to point towards impending relapse, to mobilize some type of strategy to help either fend that off or to plan for it once it's coming. Otherwise, we will be drawing bone marrows from time to time but without that extra molecular layer of precision that we have available to us now, so I think it's within our best interest to use it.

Dr. Turck:
Final question for you, Dr. Roloff.

Dr. Roloff:
Sure.

Dr. Turck:
From a high-level global view, how can CAR T-cell therapy impact our patients with relapsed/refractory B-ALL?

Dr. Roloff:
Well, I think we're coming to understand that it's a powerful therapy compared to some of the other therapies we have. I think it would be a tough case for me to make saying that the responses with blinatumomab or inotuzumab or even chemotherapy-based salvage measures for relapsed/refractory disease are going to give us higher response rates than CAR T. And so one of the things that we've thought about is the sequencing of these therapies. We're lucky in ALL, as opposed to AML, for example, where there's largely just two treatment pathways: intensive versus non-intensive therapy. But we have a lot of different weapons in our toolbox in ALL. And I think the big question is, how do we best sequence them? And are there certain patients for whom a particular order of therapies is going to matter? That ultimately begs the question of, should we be moving CAR T-cell therapy earlier?

Brexu-cel, for example, has an FDA label for, generally speaking, relapsed/refractory B-ALL. It doesn't say after two prior lines or three prior lines. We've observed, and this has been consistent with other real-world studies of CAR T in ALL, that by the time most patients are going to a CD19-directed CAR T, they've probably seen at least three, sometimes four other lines of therapy. And so the use of CAR T might be limited for some folks who simply aren't able to get there. And whether it exists along social determinants of health, of having access to a CAR T center, insurance limitations, cost of a caregiver, and the sacrifice that is required to actually go through with this process, I think there's probably a barrier for a lot of patients of never being able to make it to CAR T in the first place. And then there's other disparities that exist within the cohort of patients that actually do.

And so one of the goals that I have, and I'm going to have to see if we actually have the power statistically to do this, is to build different treatment trajectories along our dataset and figure out amongst patient A who got this sequence of three therapies and then CAR T, versus CAR T here, versus CAR T here. How can we control for some of these confounding variables, but see if there might be some role to bring CAR T up forward in our treatment trajectory and hopefully be able to leverage those same high percentage durable response rates for patients moving forward.

Dr. Turck:
Well, with those observations in mind, I want to thank my guest, Dr. Gregory Roloff, for joining me to share the latest real-world evidence and long-term follow-up data on CAR T-cell therapy for relapsed/refractory B-cell acute lymphoblastic leukemia. Dr. Roloff, it was great having you on the program.

Dr. Roloff:
Pleasure, Dr. Turck. Good seeing you.

Announcer:
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