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

From Trials to Real-World Impact: CAR T-Cell Therapy for R/R Large B-Cell Lymphoma

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:
This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Joining me to discuss the efficacy and safety of CAR T-cell therapy for relapsed or refractory large B-cell lymphoma is Dr. Matthew Matasar. He's a hematologist/oncologist and Chief of the Division of Blood Disorders at the Rutgers Cancer Institute, as well as a Professor of Medicine at Rutgers Robert Wood Johnson Medical School. Dr. Matasar, welcome to the program.

Dr. Matasar:
Thank you so much for having me today, Dr. Turck.

Dr. Turck:
So if we start with the big picture here, Dr. Matasar, how has the treatment paradigm for relapsed or refractory large B-cell lymphoma changed now that CAR T-cell therapies are moving into the second-line setting?

Dr. Matasar:
I guess what I would say there, Dr. Turck, is that we really are living through something of a true paradigm shift in the management of relapsed and refractory large cell lymphoma. And this isn't something that happens frequently in our lives as clinical investigators or even as clinicians, where we've come from a prior state where the goal of the management of a patient with relapsed or refractory large cell lymphoma was to get them to their transplant. Platinum-based chemoimmunotherapy and, for chemosensitive disease, consolidative autologous stem cell transplant was the standard of care and was really the only treatment that we felt likely to hold curative potential in this context.

All that has changed now, and we do have very compelling data from trials like ZUMA-7 and TRANSFORM that using CAR T-cell therapy in the management of relapsed or refractory large B-cell lymphoma can really improve outcomes and improve our ability to cure our highest-risk patients in a way that cytotoxic chemotherapy and autologous transplant simply did not and cannot.

Dr. Turck:
So with that background in mind, let's zero in on the available data. Pivotal trials like ZUMA-7, TRANSFORM, and BELINDA found that axi-cel and liso-cel performed better than tisa-cel, which failed to demonstrate superiority over standard therapy. How can these differences help inform which CAR T-cell therapy we select?

Dr. Matasar:
I would say that in the second-line context, we—as clinicians and as cellular therapists—really do have two tools available to us in the CAR T-cell space currently. We have axicabtagene autoleucel, or axi-cel, and we have lisocabtagene maraleucel, or liso-cel. And axi-cel and liso-cel, as you point out, were given to us in this context on the basis of the ZUMA-7 and TRANSFORM studies, respectively, both of which read out significant positive results favoring the respective cellular therapy for significant, sometimes dramatic, improvements in progression-free survival and either proven or trending differences in overall survival when using these as the intended second-line therapy instead of the prior standard of platinum-based chemoimmunotherapy with the intention of consolidative autotransplant.

Axi-cel and liso-cel, however, are not the same treatment, and they do have differences in terms of their raw absolute response rates,

CR rates, and durability. But even perhaps more importantly, there are key differences in their toxicity profiles, with significant differences in terms of the likelihood of patients experiencing overall or high-grade cytokine release syndrome, or CRS, or neurological side effects of treatment called ICANS.

Dr. Turck:
So that gets to my next question about safety related to CRS and ICANS, which are common adverse events. How are early intervention strategies evolving to help mitigate these risks?

Dr. Matasar:
It's a great question, and it's important to recognize that there is ongoing evolution in our ability to deliver CAR T-cell therapy in the second-line setting safely and effectively. We know, for instance, that using axi-cel is associated with very high rates of cytokine release and moderately high rates of neurological toxicities. But very straightforward interventions, such as prophylactic dexamethasone, can really help mitigate the frequency and severity of each of these two toxicities without having an impact on efficacy of the delivered CAR T-cell therapy.

There's even an ongoing question of: can we improve upon prophylactic dexamethasone, particularly for patients who may be at heightened risk for neurological toxicities, with the use of prophylactic anakinra? And work that's been led by Jae Park at Memorial Sloan Kettering and others has shown that prophylactic anakinra—before the onset of neurological toxicities—can indeed lower the frequency and severity of neurological toxicity with CAR T-cell as well. So we're continuing to work hard in the clinic and in clinical trials to develop strategies to mitigate the toxicities that may limit our ability to deliver this curative therapy.

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. Matthew Matasar about the latest efficacy and safety data on CAR T-cell therapy for relapsed or refractory large B-cell lymphoma.

Now, if we take a look at real-world data, registries like the Center for International Blood and Marrow Transplant Research and the European Society for Blood and Marrow Transplantation suggest that patients in the real-world settings—who are often older and have more comorbidities—can achieve outcomes comparable to their clinical trial counterparts. However, they tend to experience more grade 3 or higher adverse events. So, Dr. Matasar, how do these findings influence patient counseling and monitoring?

Dr. Matasar:
It's fascinating to me to see the real-world evidence evolving for the use of CAR T-cell therapy. It has been truism in lymphoma and broadly in oncology that real-world evidence underperforms compared to clinical trial settings because patients are often less fit, more frail, have more comorbidities, and may have disease tempo or burden that is dissimilar or disadvantageous compared to the more pristine population enrolled in prospective clinical trials.

This has not been the case with the CAR T real-world evidence coming out of either the United States or Europe, where efficacy of these key therapies is really quite similar, even when taken to a broader, more comprehensive, and less restricted population as seen in real-world evidence. It's deeply encouraging and reinforcing for me as a clinician—let alone a researcher—to see that these data hold up in the wild, so to speak.

The toxicity data is real, and that's to be expected in part because the centers that are delivering CAR T to these patients may not be the ones that are as comfortable with the use of CAR T versus the ones that are being engaged in the prospective trials. But it also may have something to do with the underlying protoplasm, as we'd say, of the patients where they do have more comorbidities or may have a higher burden or more rapid pace of disease—all of which we know from models like CAR-HEMATOTOX are going to be associated with heightened risks of experiencing toxicities.

But as we were discussing, we are developing strategies to mitigate, ameliorate, or intervene early upon these toxicities. And I would say that the more comfort that we gain as a discipline in the use of CAR T and in these associated supportive strategies, the more broadly we will be continuing to define what it means to be eligible for CAR T-cell therapy and be able to give this treatment to more patients and hopefully improve outcomes at the broader level.

Dr. Turck:
In the final few moments that we have here, I'd like to focus on logistics. Timeliness is a critical success factor, but we often encounter delays in treatment. Would you tell us about some of the key barriers you've seen and how we can work to streamline access to CAR T-cell therapy?

Dr. Matasar:
It's a very important question, particularly when we recognize that in some ways, it is the logistical barriers that have created the

greatest barrier to broadening the ability at the national or global level to deliver these treatments to patients.

If you think about the journey from a patient experiencing the relapse or being identified with primarily refractory large cell lymphoma to they're actually receiving the CAR, there's a number of steps in that journey that need to be addressed in order for this to be streamlined. The first is in the referral itself, trying to get that patient in front of a physician who's CAR-enabled. And we've seen tremendous headway in developing closer relationships and collaborative structures between community oncologists, where the majority of patients in the United States continue to receive their treatment, and CAR T centers, where community oncologists and their referring CAR T center are able to develop closer ties and streamline the referral process to enable patients to be seen promptly.

Dr. Turck:
So then if we're able to overcome those logistical hurdles and ensure CAR T is delivered both safely and efficiently, what kind of impact could that have on our patients with relapsed or refractory large B-cell lymphoma?

Dr. Matasar:
I would say that it's a problem for us in the United States, currently, that only a minority of patients who would potentially or theoretically benefit from treatment with CAR T go on to receive this treatment. Estimates place this number at about 1 in 4 to 1 in 5. We're behind some of our European colleagues in this, where rates of CAR T-eligible patients receiving CAR T are closer to 40 to 50 percent. And we need to do better. We can do better. But addressing the logistical barriers from referral to hastening access to apheresis and improving our treatment abilities in the holding or bridging stages in the patient journey can help ensure that more patients are able to get it from what we call “brain-to-vein time,” when we think about what patient may need CAR to the actual delivery of the CAR.

Dr. Turck:
Well, given those impacts, I want to thank my guest, Dr. Matthew Matasar, for joining me to talk about how we can optimize CAR T-cell therapy for patients with relapsed or refractory large B-cell lymphoma. Dr. Matasar, it was great having you on the program.

Dr. Matasar:
Dr. Turck, thank you for the opportunity.

Announcer:
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