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Optimizing Second-Line CAR T Decisions in 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. Here with me today to discuss the evolving therapeutic landscape for relapsed/refractory large B-cell lymphoma and how it can impact our treatment decisions is Dr. Sairah Ahmed. She's an Associate Professor in the Department of Lymphoma and Myeloma, with a co-appointment in stem cell transplant at the MD Anderson Cancer Center, where she's also the CAR T Program Director in the Department of Lymphoma and Myeloma. Dr. Ahmed, welcome to the program.

Dr. Ahmed:
Thank you. Pleasure to be here.

Dr. Turck:
Well, to start us off, Dr. Ahmed, how has the second-line treatment for relapsed/refractory large B-cell lymphoma evolved in recent years?

Dr. Ahmed:
So I think it's actually been a paradigm shift in the way that we treat patients who have early relapsed lymphoma. Traditionally, what would happen is patients would receive some kind of salvage chemotherapy, and about half of them would have disease response that would allow them to then proceed to an autologous stem cell transplant. Many patients did not have disease that would respond, or they were ineligible for transplant due to comorbidities or other factors.

With the advent of CAR T-cell therapy, particularly with the trials that confirmed an overall survival benefit for CAR T-cell therapy in the second line, there has been a shift to utilize CAR T-cell therapy for patients who have disease that relapses within the first 12 months after completion of therapy, disease that does not respond to frontline chemotherapy, or patients who would otherwise not be eligible for autologous stem cell transplant.

I think it's actually kind of hard to look at it at this point and realize how far we've come from the time where patients would have primary refractory disease that did not respond, and after the second-line setting, we would start to talk about palliative care. And really, these patients now have a curative-intent treatment. So there's been a huge change in the way that we treat these patients.

Dr. Turck:
Now, continuing to zero in on CAR T-cell therapy, what clinical factors help determine whether a patient is an ideal candidate?

Dr. Ahmed:
So that's a really good question because there are both disease-related factors as well as patient performance status—how well they're doing and their comorbidity status. The clinical trials, both ZUMA-7 as well as the TRANSFORM trial, confirmed that, number one: Axi-cel or Liso-cel, both of those CAR T products that have been approved in the second line, do better than the standard, which was salvage chemotherapy followed by autologous stem cell transplant. But they had fairly narrow eligibility criteria, and so there has been a ton of work looking at real-world analyses to try to determine which patients are going to benefit from this therapy beyond those that were treated in the trial. And what we've seen is that patients who have comorbidities are still eligible for CAR T-cell therapy. Those that traditionally are not considered eligible for stem cell transplant are eligible for CAR T-cell therapy; patients with reduced renal function,

patients with CNS lymphoma and patients who have cardiac dysfunction, lung dysfunction, or even liver dysfunction can all be eligible.

Now, the toxicity profile might look a little bit different. They're certainly at a higher risk for some of the side effects. We would watch them more carefully. But really, those are the patients who are also going to receive the most benefit because they have limited other options. And the real-world analyses, both here in the United States as well as over in Europe for both of these products, have demonstrated that the overall response rate and the complete response rate are very similar. And what that means is that the patients who were very well selected on the clinical trials are doing the same in terms of outcomes as patients who would not be eligible for those clinical trials.

In terms of factors for patients as we're treating them, I think what the thing that would be most important to look at is response to treatment. So for patients who are receiving frontline chemotherapy, how are they responding to that chemotherapy? If the first restaging scan—PET scan or CT scan—shows that the response is not ideal, that would be the time point to start to think about looking at CAR T-cell therapy in the future. Absolutely, if they have an end-of-treatment scan that shows persistent disease, those patients should also be referred to CAR T-cell therapy early.

Dr. Turck:
Now, in addition to those clinical indicators, are there any biomarkers that can help us identify high-risk patients who might benefit from an expedited evaluation and referral?

Dr. Ahmed:
So I think some of this is still in the clinical trial phase, but particularly, ctDNA post-completion of therapy may be a marker that will help us to determine which patients are destined to have disease return. And so one of my colleagues, Dr. Jason Weston, is heading up a trial that is looking at that feature—so patients who have a complete response on a PET scan but monitoring their ctDNA soon after they complete therapy, and then offering a clinical trial that would use CAR T-cell therapy for patients who have positive ctDNA. And I think that is one of the ways where potentially, we can really give people the benefit of CAR T-cell therapy early on, with decreasing some of the side effects and toxicity because a lot of the toxicity surrounds tumor bulk. So if you have big, bulky lymphoma that's progressing quickly, you tend to have more side effects associated with the CAR T-cell 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. Sairah Ahmed about how we can optimize strategic decision making when caring for patients with relapsed/refractory large B-cell lymphoma.

Now, Dr. Ahmed, even though guidelines from expert panels like the NCCN support early referral, real-world studies show that there continue to be delays in delivering CAR T-cell therapies. So what are some of the most common barriers you see in clinical practice?

Dr. Ahmed:
So I think one of the barriers that is very difficult to overcome is that CAR T-cell therapy is generally offered in urban areas, and in large parts of the country, people don't live close to those urban areas. And the second is in regards to the guidelines around CAR T-cell therapy. So in the past, you had to move to a CAR T center and be able to be within 2 hours of that center for at least 30 days. You had to have somebody who was going to be your caregiver 24/7 for that entire time period, and patients were not allowed to drive for 8 weeks post-CAR T-cell therapy.

Now, those guidelines were put in place because the toxicity profile of CAR T-cell therapy is very different than regular chemotherapy. Actually, it's more in line with stem cell transplant. We have some of the same guidelines associated with transplant about staying next to the center where you get the transplant. But the hardship, both financial as well as emotional, on patients to have to do such a big move in the middle of also dealing with relapsed cancer can be quite fatiguing and overwhelming. And while insurance companies may pay for the actual procedure, there are limited resources to pay for transportation, housing, and food. Oftentimes, the person who is your caregiver is also the person who has the job that gives you the insurance to be able to pay for CAR T-cell therapy. So all of those things become a complex network, and so although I'm sure many oncologists will talk to patients about CAR T-cell therapy, I think patients get quite overwhelmed when hearing about all the steps required.

And then, there's just the logistics, right? So if someone is living 5 hours away from a CAR T center and they have to have a referral and then come to that CAR T center to be able to be seen and all of the subsequent steps need to happen only at that center, it makes it just much more challenging to do.

Recently, there have been changes in the FDA guidance about both the REMS requirement, which is the follow-up associated with CAR T-cell therapy, as well as some of the restrictions in access after real-world data has been published showing that most of the toxicity happens within the first 14 days. And so for certain eligible patients, they may actually be able to go home at 2 weeks and they may be

able to start to drive at 2 weeks. While they will still need a caregiver close to them at home, they should be able to go back, generally, to normal lives. And I think that that will greatly improve access. And maybe it will just improve people going to that first referral to be able to understand what CAR T-cell therapy is and not feel like it is an out-of-reach therapy for them.

Dr. Turck:
And how could strategies or tools like automated EHR referral flags help us streamline patient identification?

Dr. Ahmed:
So I think there are multiple tools that could help both identify patients within certain networks of cancer care as well as help to expedite their referrals and intake into CAR T centers. For example, at our center, if we have a patient who either self refers or has a local physician who refers them and anywhere on the chart or on the message says CAR T-cell therapy, it automatically goes to a different group of people for intake to be able to make sure that that patient comes in the door as fast as we possibly can and decrease delay. And the reason that's important is that there are studies that have shown that when you have patients receive CAR T-cell therapy faster, particularly if we could get CAR T-cell therapy in the second-line setting versus the third-line setting, both outcomes are better, toxicity is better, and patients recover faster. So trying to utilize both electronic as well as human ways to expedite patients getting into CAR T-cell therapy centers, I think, is going to be important.

I think the other part of that is education. So as patients are receiving their frontline therapy, one of the questions that we always get is, what if this doesn't work? What would be the next step? That would be a good time to say, God forbid, if this treatment doesn't work, let's talk about all the other options, one of which is CAR T-cell therapy. And if that happens, then we're going to refer you to our closest center and our partners, and that way the patient knows that if that comes to be, then we really need to move quickly.

Dr. Turck:
And before we close, Dr. Ahmed, looking at the big picture, if we overcome a number of those barriers and start to implement timely referrals on a wider basis, how could that impact outcomes of our patients with relapsed/refractory large B-cell lymphoma?

Dr. Ahmed:
Yeah. So I think that it's very important for us to know that there is an overall survival benefit for CAR T-cell therapy in the second-line setting. So the ZUMA-7 trial with axicabtagene ciloleucel demonstrated that patients live longer. And I think for oncologists, that's our gold standard, right? That's what we want for every one of our patients. We want to choose the treatment that's going to have the opportunity to give them benefit, to live longer, and to go back to their lives. And so there's going to potentially be a group of people that will be cured of their lymphoma by CAR T-cell therapy if they can get to it fast enough and efficiently enough. And that would, potentially, help to preclude any further treatment and also make them able to go back to their normal lives, jobs, families, etcetera. So the impact I think is huge. But it's going to require quite a bit of coordination and collaboration between patients, their physicians, and CAR T centers.

Dr. Turck:
Well, given that potential impact, I want to thank my guest, Dr. Sairah Ahmed, for joining me to discuss the importance of treating relapsed/refractory large B-cell lymphoma early in the setting of second-line therapy. Dr. Ahmed, it was great having you on the program.

Dr. Ahmed:
Thank you.

Announcer:
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