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Managing B-Cell Lymphomas in the Second-Line Setting: The Role of CAR T-Cell Therapy

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Kite Pharma, a Gilead Company. Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
This is *Project Oncology* on ReachMD, and I'm your host, Dr. Jennifer Caudle. And joining me today to discuss CAR T-cell therapy for the management of B-cell lymphomas in the second-line setting is Dr. Sarah Rutherford. She's an Assistant Professor of Medicine in the Division of Hematology-Oncology at Weill Cornell Medicine. Dr. Rutherford, welcome to the program.

Dr. Rutherford:
Thank you so much, Dr. Caudle. I'm really excited to be here today to talk about CAR T-cell therapy, which is making a huge difference for our patients.

Dr. Caudle:
Well, we're definitely excited to hear your insights. So to start us off, Dr. Rutherford, can you give us an overview of CAR T-cell therapy and how it works as a targeted approach for B-cell lymphomas?

Dr. Rutherford:
CAR T-cell therapy is really an immunotherapy approach that is now FDA approved in a number of different lymphoma types. But I'm really going to talk specifically about diffuse large B-cell lymphoma, which is where we initially had an approval for this type of drug. So essentially, it involves a collection from a patient. Basically, blood is collected from a patient and sent to one of the companies who manufactures these T cells. They manufacture them in such a way that they both target CD19, which is a protein on the surface of the B cells as well as the T cells. And then it usually takes between 2 to 3 weeks for this process to be done. And then it is sent back to the hospital where it is infused in patients who have lymphomas who haven't responded adequately to first-line therapy and allows us to use a new strategy to better fight the lymphoma.

Dr. Caudle:
And which of our patients are eligible to receive this therapy and when?

Dr. Rutherford:
That is a great question because it has really evolved, and I think it will continue to evolve. But again, I'm going to speak specifically about diffuse large B-cell lymphoma. That's the most common lymphoma type. It's an aggressive disease. And traditionally, the management was for patients who don't respond adequately to the first-line therapy would be a second-line type of chemotherapy followed by autologous stem cell transplant. But essentially now, for patients who have received a first line therapy, such as R-CHOP, that haven't responded adequately or in which the disease has returned within a year, those patients are now eligible to receive CAR T-cell therapy. So just to give you an example, if I have a patient who is actually in the middle of the treatment course or towards the end of the treatment course and we do an imaging test to assess the response and we find that the disease is still there, we would then really think about this CAR T-cell therapy for those patients.

Again, it's a really great option because the data support that the traditional chemotherapy drugs just aren't as effective as we want for these patients. We have data that the CAR T-cell therapy for patients in the second-line setting for diffuse large B-cell lymphoma is more effective than the older strategy with the autologous stem cell transplant.

Dr. Caudle:
That's very helpful. And so with that background in mind, let's turn our attention to its efficacy. How does CAR T-cell therapy impact patients with B-cell lymphomas in a second-line setting?

Dr. Rutherford:
It's a great question. So traditionally, there have been a number of studies that have looked at patients who actually didn't respond to third-line therapy. Unfortunately, their overall survival would be very short, like on the order of 4 to 6 months. So we really want to try to use novel treatments as early as possible for these patients to try to prevent us from getting into a situation where someone is in a third line and needing another treatment and knowing that their prognosis isn't great. So I've alluded to some studies already. There were actually two different clinical trials that were both reported in the last couple years. One was called ZUMA-7 and the other one was called TRANSFORM. And both of these studies involved a CAR T-cell product that targeted CD19.

Those products were axi-cell and liso-cel, and basically, they randomized patients with diffuse large B-cell lymphoma who had an inadequate response to the first-line therapy, which is often R-CHOP. And so either they didn't respond adequately or the disease returned within a year, and these patients were randomized to either the older type of treatment, which was a second-line chemotherapy followed by autologous stem cell transplant, versus the CAR T-cell therapy. And there were some difference in these trials, but essentially, both the ZUMA-7 and TRANSFORM studies showed an improvement in event-free survival on the order of about 6 months for ZUMA-7 and about 8 months of a difference for TRANSFORM between the standard of care, which was the autologous stem cell transplant versus the CAR T-cell therapy.

So really a marked difference in terms of the patient's response to the new therapies. And that's really why these two different products have become FDA-approved in the second-line setting for patients with diffuse large B-cell lymphoma.

Dr. Caudle:
And as a quick follow up, can you share some key clinical data demonstrating the efficacy and impacts of CAR T-cell therapy for relapsed or refractory B-cell lymphoma?

Dr. Rutherford:
As clinicians, we like to hear complete response rate. We like to think about different parameters, but specifically, I think that really sticks in my mind with both the ZUMA-7 and the TRANSFORM studies that there was a complete response rate of about mid 60s for both of those trials with their CAR T-cell product versus in the 30s for patients with a standard second-line chemotherapy and autologous stem cell transplant. Now I think the key that's going to be the most important for us moving forward is what is the durability of this type of response? Because obviously CR is great and that's what we want, but we also want that CR to be staying for the next year, 2 years, 3 years, etc.

But again, it's really exciting. We have so much optimism because we have this new therapy with better outcomes. And so to me, that's what is making the biggest difference for me as a physician.

Dr. Caudle:
For those of you who are just joining us, this is *Project Oncology* on ReachMD. I'm Dr. Jennifer Caudle, and I'm speaking with Dr. Sarah Rutherford about the role of CAR T-cell therapy in the management of B-cell lymphomas in the second-line setting.

So now that we've reviewed the efficacy of CAR T-cell therapy, Dr. Rutherford, let's zero in on its safety profile. What adverse events should we be on the lookout for?

Dr. Rutherford:
There are two main adverse events that we particularly watch for as being some of the ones that could be the most concerning or the most serious type of issues that could come up. And those are called cytokine release syndrome and neurologic toxicity. So I'll talk first about cytokine release syndrome. This is basically an inflammatory response that happens in many cases when patients receive CAR T-cell therapy. Many of the CAR T-cell products are actually administered in the hospital setting because we're monitoring really closely for these types of issues. So basically from a clinical standpoint, when someone has cytokine release syndrome, it can look like sepsis, like it's an infection. People can get fevers, low blood pressure, high heart rate, and low oxygen. I think it's very important to be in close touch with our ICU colleagues because sometimes these patients end up needing to go to the ICU. As with any toxicities within our field, there are different grades of that. And so many times when people do get this type of toxicity, it's low grade, so it doesn't necessarily require any major intervention. It may require fluids, but it usually doesn't more often than not. It would require just close monitoring on the hospital floor rather than requiring transfer to the ICU setting. But that does happen sometimes. So both of the products that we've been talking about have had some cytokine release syndrome observed, but relatively low grade for the most part.

And then the neurologic toxicity is variable. It can be very minor, just like a little bit of fatigue or a little bit of slow thinking. It can

sometimes be more severe. And so actually what we do, and I think most hospitals do, is have our neurology colleagues see the patients even ahead of time before they get the CAR T-cell product basically as a pre-exam to make sure we know what their baseline is. We do MRIs of the brain to just make sure they don't have lymphoma involvement and/or other issues that we need to be watching for. I think in these different products that are now approved, there are some neurologic toxicities that have been seen, but they have tended to be lower grade and very manageable and almost always reversible when that happens.

Dr. Caudle:
We've covered a lot today, but before we close Dr. Rutherford, I'd like to ask if you have any final thoughts on CAR T-cell therapy for patients with relapsed or refractory B-cell lymphoma?

Dr. Rutherford:
Well, I do want to note the CAR T-cell therapy in diffuse large B-cell lymphoma was initially approved in the third-line setting. And we still do use it in that case. And sometimes, for example, someone has already had an autologous stem cell transplant, say three years ago before this was approved, and then they relapsed. And so CAR T-cell definitely does still have a role in the third line and later as well. I think the other exciting point is seeing where this may end up in the algorithm. For example, there are clinical trials that are ongoing which are looking at incorporating CAR T-cell more in the first-line setting, perhaps enrolling people with newly diagnosed diffuse large B-cell lymphoma. And if they have an inadequate response determined very early in the process, then go straight on to getting a CAR T-cell product rather than waiting until later. Knowing the historical data of the poor outcomes of people when they get to the third- and fourth-line settings, I'm really excited about the concept of this type of product being used even earlier in the treatment algorithm for patients with diffuse large B-cell lymphoma.

Dr. Caudle:
Well, with those final thoughts in mind, I'd like to thank my guest, Dr. Sarah Rutherford, for joining me to discuss CAR T-cell therapy as a second-line standard of care for patients with relapsed or refractory B-cell lymphoma. Dr. Rutherford, it was great having you on the program.

Dr. Rutherford:
Thank you so much. I really enjoyed it.

Announcer:
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