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Advances in Follicular Lymphoma Treatment: CAR T-Cell Therapy's Evolving Role

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

Dr. Turck:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and joining me to talk about the evolving role of CAR T-cell therapy in follicular lymphoma is Dr. Jonathan Cohen. Not only is he a Professor in the Department of Hematology and Medical Oncology at the Emory University School of Medicine, but he's also the Co-Director of the Lymphoma Program at the Winship Cancer Institute of Emory University in Atlanta. Dr. Cohen, thanks for being here today.

Dr. Cohen:
Thank you very much for having me. It's my pleasure.

Dr. Turck:
Well, to set the stage, Dr. Cohen, would you explain how CAR T-cell therapy changed the treatment landscape for follicular lymphoma, especially when we compare it to previous approaches?

Dr. Cohen:
Sure, absolutely. So CAR T-cell therapy, which is an immunotherapy that—at least in lymphomas—targets CD19, has been around now for several years. It was initially developed as an approach for the management of patients with aggressive lymphomas that had recurred after therapy, and it really revolutionized the way we think about managing patients in that situation.

Follicular lymphoma is a little bit of a different disease. It is more of a low-grade lymphoma. It tends to recur over a prolonged period of time. And so initially, there wasn't necessarily the expectation or the thought that this type of approach was something that was going to be critical for patients with follicular lymphoma.

But as many of your listeners likely know, there are plenty of patients that we see with follicular lymphoma that while we expect them to experience prolonged progression-free survival, unfortunately their disease recurs and may recur multiple times and can become increasingly difficult to treat. And so that's why the availability of CAR T therapy—not just for aggressive lymphomas, but also for follicular lymphomas—has really changed the way we think about managing patients who have multiply-relapsed disease or who otherwise have higher-risk features where we have historically not had the same success at treating them. Whereas before we might have to commit somebody to pretty much lifelong therapy, which can accumulate toxicity over time, CAR T, although it can be somewhat intense at the beginning, is a one-time treatment, which in follicular lymphoma has resulted in many patients achieving very long and durable remissions.

Dr. Turck:
Would you walk us through the significance of those outcomes and how they should be interpreted in the follicular lymphoma setting?

Dr. Cohen:
Of course. So as I mentioned, patients with follicular lymphoma, in most cases, are going to have a disease that responds very well to treatment and will enjoy a prolonged period of time without recurrence. However, we know that there are patients who either have early recurrence within 2 years or who have multiple recurrences where that experience is not what we see. And unfortunately, in the past,

many of those patients, even if they were to receive additional therapy, would not have the same depth of response that we would hope to see, and that could result in prolonged survival.

Dr. Turck:
Now, given that, as you mentioned, follicular lymphoma often follows a more indolent course, how should we begin to think about the optimal timing for CAR T, particularly in patients who might not need immediate and aggressive therapy?

Dr. Cohen:
Yeah, so this, I think, is really the key question. So the majority of patients that I see with follicular lymphoma will never need something like CAR T therapy. And just for those who aren't as familiar, when we talk about administering CAR T therapy, what we're talking about is a patient coming in first to complete apheresis, where their T cells are removed. Then there's a manufacturing process, and then there's an infusion and a follow-up process. So for a good period of a couple of weeks to months, they are spending a good amount of time at the cellular therapy center, and this can be quite disruptive. So for a patient with a chronic disease where, more often than not, they're going to enjoy prolonged progression-free survival even without CAR T, this is a big step to have to take.

And so for me, one of the things that is constantly on my mind when I'm evaluating a patient with follicular lymphoma is whether this is a patient that has high-risk features? Is this a patient who has not responded the way we would have expected to our most active available therapies? Is this somebody who is not tolerating chronic therapy and who might be better served by a single, more intensive treatment as opposed to staying on ongoing therapy for whatever reason—whether it be toxicity, financial considerations, or whatnot?

So I think these are all things that have to be taken into account. I'm certainly not suggesting that every patient with follicular lymphoma should be evaluated and managed with CAR T. But for those patients that are clearly demonstrating a disease phenotype that is different than what we would have expected or more aggressive than what we would have expected, I do think it's important to discuss CAR T and bring it up somewhat early in the course so that you can make sure that you have time to get everything in place if, ultimately, you feel like it's an appropriate option for that patient.

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. Jonathan Cohen about how CAR T-cell therapy is changing the way we treat follicular lymphoma.

Now, as with any treatment, Dr. Cohen, safety is always a consideration, especially in a disease where, as you mentioned, patients could potentially live for many more years after being diagnosed. So what do we currently know about the long-term toxicity profile of CAR T in follicular lymphoma?

Dr. Cohen:
So fortunately, most patients who complete CAR T therapy are going to do just fine with the treatment, are going to recover fully, and hopefully are going to go back to their normal life in remission for an extended period of time. But as you point out, just like with any treatment, there can be toxicities. And especially in a patient who may not be having a lot of symptoms related to the disease itself, you want to really make sure that you're doing everything you can to mitigate those risks and to limit those toxicities.

In the short term, the main things that we run into with this type of therapy are toxicities related to the interaction of the CAR T therapy with the patient's immune system. So this can be something called cytokine release syndrome, or CRS, where they have a high fever, low blood pressure, and really look as if they're experiencing sepsis. That's the way it presents. And there also can be neurologic toxicities, which can be subtle but can be problematic. They also require observation and management. And so these are all things that our team—and that any cell therapy team—is adept at monitoring for and managing. And to be honest, those are not the types of things that I am most concerned about going into CAR T because I know that that is a short-lived experience and something that we can address.

What I do worry about more are some of the longer-term issues that we have seen with CAR T therapy. One of the biggest challenges is that many patients who receive CAR T will have prolonged cytopenias and may require growth factor on a number of occasions or may require ongoing transfusion support for blood and platelets. And this can really become problematic for patients because even though you might be able to manage them, it becomes challenging to get back to a normal life when you are neutropenic and are having to be mindful about infectious risk or when you're having to come every week or 2 for transfusion support and in between are developing fatigue or bleeding complications. And so one of the things that we really try very hard to pay attention to early on is whether or not patients are experiencing that type of complication.

The other thing that we do see with CAR T is that patients can have prolonged hypogammaglobulinemia. And this, again, can increase their risk of infections, which—although not necessarily life-threatening—can be very bothersome and burdensome to a patient's quality

of life. And so for patients that I'm following that are now 6 months, 12 months, or 18 months and beyond that have had CAR T, the main issue, if they're having a problem, is usually related to one of those two things, and those are things that have to be considered when you're evaluating patients.

Dr. Turck:
And as new therapies enter this space, like bispecific T-cell engagers, how do you see the treatment landscape evolving? And do you think these new agents will compete with or complement CAR T?

Dr. Cohen:
Also a great question that I think we, at least at present, don't necessarily know the answer to. What I would say, though, is that the BiTEs, or bispecific T-cell engagers, have really changed the way we think about managing patients with recurrent disease, both in aggressive lymphomas as well as in low-grade lymphomas. These are highly active, and we have seen patients achieve deep and durable remissions; they're often able to discontinue therapy and maintain that remission.

I think that there are clear reasons that you might choose one approach over the other. So although the BiTEs don't necessarily require treatment at a cell therapy site and don't require the manufacturing process—they can be given off the shelf—they do require ongoing treatment over a prolonged period of time. And so a patient has to be able and willing to receive more of a chronic therapy as opposed to CAR T, which is a single infusion. In addition, the BiTEs themselves also can have toxicities, which can include infectious complications. And also, patients are at risk for CRS and neurologic toxicity with BiTEs. So I wouldn't say that they are an easy option, but certainly, they are a good option.

One other thing that we've seen is that the BiTEs can be safely combined with other therapies. And there's, in fact, interest in looking at them in the front-line or earlier on in the course of treatment. My guess would be that, when all is said and done, most patients that have recurrent disease may ultimately receive both at some point over the course of their treatment.

Dr. Turck:
And before we wrap up, Dr. Cohen, let's look ahead for just a moment. Are there any emerging strategies or clinical trials you're excited about that could change how we use CAR T in follicular lymphoma?

Dr. Cohen:
So I think where the field is really going is trying to see if we can utilize some of these immunotherapies earlier on in the course of treatment, whether that would be in the frontline setting or in patients who experience an early recurrence or who perhaps have residual disease at the conclusion of therapy. Now, in follicular lymphoma, fortunately, that is less of an issue compared to what we see in aggressive lymphomas. So I don't know if, at least in the short term, we're going to be integrating CAR T in the frontline setting. It certainly is being considered and is something that again, for high-risk patients or patients with inadequate response, we may want to think about.

But generally speaking, where we really are seeing a lot of improvement, number one, is in the ability to combine immunotherapies with other standard treatments to better identify who are the patients that stand to benefit the most. And also, we are trying, at least, to learn more about how best to mitigate toxicities. And those are all things that I think are going to make CAR T more accessible for additional patients as time goes on.

Dr. Turck:
Well, as those forward-looking thoughts bring us to the end of today's program, I want to thank my guest, Dr. Jonathan Cohen, for joining me to discuss the role and impact of CAR T-cell therapy in treating patients with follicular lymphoma. Dr. Cohen, it was great having you on the program.

Dr. Cohen:
Thank you so much for having me.

Announcer:
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