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

Considering CAR T-cell Therapy in Follicular Lymphoma

Announcer:
You're listening to *Medical Breakthroughs from Penn Medicine* on ReachMD, advancing medicine through precision diagnostics and novel therapies. Here's your host, Dr. Charles Turck.

Dr. Turck:
Patients with follicular lymphoma who relapse or don't respond to treatment typically have a poor prognosis, and unfortunately, there aren't many treatment options available to them. But could the recent FDA approval of a chimeric antigen receptor T-cell therapy, or CAR T-cell therapy for short, help change all that?

Welcome to *Medical Breakthroughs from Penn Medicine* on ReachMD. I'm Dr. Charles Turck, and joining me today to discuss what the recent CAR T-cell approval could mean for patients with relapsed or refractory follicular lymphoma is Dr. Elise Chong. She's an Assistant Professor of Medicine and Associate Director of the Lymphoma Clinical Research unit at Penn Medicine's Abramson Cancer Center. Dr. Chong, welcome to the program.

Dr. Chong:
It's great to be here.

Dr. Turck:
So let's begin by taking a look at the current treatment landscape for follicular lymphoma. Dr. Chong, what treatment options are available for these patients?

Dr. Chong:
To place this FDA approval in perspective, I think it helps to understand a little bit about the natural history of follicular lymphoma. So typically, it's a slow-growing, indolent B-cell lymphoma that we think of as not usually curable, and managed as a chronic disease. And for relapsed or refractory follicular lymphoma, there are actually many treatment options, the choice of which is informed by a patient's prior therapies. And so these include monoclonal antibody therapy alone – usually targeting CD-20, chemotherapy with or without monoclonal antibody therapy lenalidomide rituximab, PI-3 kinase inhibitors, ADH2 inhibitors, and of course, CAR T-cell therapy and variants consisting of hematopoietic stem cell transplantation. But traditionally, the duration of disease control comes shorter and shorter as patients require additional lines of therapy, and also some of these therapeutic options, especially in the later line settings, have relatively short durations of response.

Dr. Turck:
Given the limited options available for relapsed or refractory follicular lymphoma, let's turn our attention to the FDA's most recent CAR T-cell therapy approval. What could you tell us about that?

Dr. Chong:
So, tisagenlecleucel is a type of CAR T-cell therapy. This allows us to genetically engineer a patient's T-cells to specifically target a specific antigen, in this case CD-19 which is expressed on all B-cells, but also follicular lymphoma cells. And this is actually the third indication for tisagenlecleucel. The first two were in ALL as well as aggressive B-cell lymphomas. But this past May, tisagenlecleucel received accelerated approval from the FDA for adults with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy. And this approval for follicular lymphoma is really exciting because of the promising data that we have in CAR T-cell therapy for follicular lymphoma. Although I just told you that there is a litany of other treatment options it's exciting because it has a relatively good

safety profile, and we have long-term follow-up data that look really promising for this product.

Dr. Turck:
And if we zero in on the data that led to this recent FDA approval, would you share some of the key findings from the study investigating the therapy?

Dr. Chong:
Sure. So this was based on the ELARA trial which was an international phase 2, open label trial that enrolled just under 100 patients with follicular lymphoma, grades 1 through 3A. And these patients were pretty heavily pretreated. They had a median of four prior lines of therapy and with generally what we think of as poorer prognosis disease. Sixty percent of them had bulky disease. All of them had received prior anti-CD20's and alkylating agents and two-thirds of them were refractory to both an anti-CD20 and an alkylating agent, which is also a poorer prognosis.

The median follow-up was about a year and a half, and the overall response rate was 86 percent, with a complete response rate of 69 percent. With CAR T-cells, we always worry about what the toxicity profile is, and about half of patients had cytokine release syndrome, but there was no reported high-grade cytokine release syndrome, meaning grades 3 or higher, and very few high-grade neurologic events, which is the other major complication of CAR T-cells that we worry about. Furthermore, there were no treatment-related deaths, which is something that we've seen in some of the other trials. And of those patients who had a complete response at 12 months, about 85 percent remained in complete response, so that's really great in that relapsed/refractory setting.

Dr. Turck:
For those just tuning in, you're listening to *Medical Breakthroughs from Penn Medicine* on ReachMD. I'm Dr. Charles Turck, and today I'm speaking with Dr. Elise Chong about CAR T-cell therapy for relapsed or refractory follicular lymphoma. So, Dr. Chong, now that we know more about what led to this recent FDA approval, how do you think CAR T-cell therapy will impact patients with relapsed or refractory follicular lymphoma?

Dr. Chong:
So, I think there are two components to this question. One is who's going to really benefit from this even within the relapsed/refractory follicular lymphoma populations? And two is, how much do they really benefit? As I talked about earlier, there's a huge range of expected natural history with follicular lymphoma. Essentially, a really broad prognosis and some people will do really well with minimal therapy, and others really need very specific therapies. And so selecting the appropriate patients for treatment is really critical. We know that patients with progression of disease within two years after front-line chemoimmunotherapy have a four or five-year overall survival prognosis, and this is about 20 percent of patients with follicular lymphoma. So I think that group would certainly benefit from CAR T-cell therapy.

There's also a group of patients that are double refractory. And that's refractory to an anti-CD20 antibody and an alkylating agent but also generally have a poorer prognosis and much shorter responses to later-line therapies. And then, just in general, patients who are heavily pretreated and younger patients for whom we really need therapies that are going to be long-lasting, I think those are the groups that are really going to benefit the most. One of the major questions that remains is what's the duration of benefit to CAR T-cells, because obviously, if follicular lymphoma is a disease that has a very long expected, natural expected prognosis how long does this treatment really work?

And so, our group at Penn including both the Center for Cellular Immunotherapies, as well as the Lymphoma Program conducted the initial work on the product that would later become tisagenlecleucel. And so this was work that was initially published in the New England Journal by Steve Schuster, and we recently reported our five-year outcomes in 2011 which is the longest follow-up to date for this product. And we found that at five years for patients with follicular lymphoma, the median duration of response was still not reached, and actually about 60 percent of those patients had a sustained response at five years. And this group of patients was as much, if not more, heavily pretreated than the group for which the FDA approval was based. I'm really optimistic that this is going to make a major impact in patients' lives.

Dr. Turck:
Now if we take a moment to look at the manufacturing process, we know it's a time-consuming and costly one. So with that being said, are we any closer to addressing those challenges?

Dr. Chong:
Yeah, so there are multiple approaches. One is to use allogeneic CAR T-cells, so this would basically enable us to have an off-the-shelf option to patients, that basically would be readily available so we wouldn't have to have the current delay to manufacture the T-cells and potentially also could decrease cost, if we have a product that's available to all patients without needing the additional time to collect T-

cells, and then manufacture them. And while this concept is really exciting, and I think where the field is headed this approach is still in the development phase, so we don't currently have it yet. Another approach is to shorten the manufacturing time for autologous CAR T-cells, which is also under way.

Dr. Turck:
And before we close, let's look to the future for just a moment. Given that this is the third approval for CAR T-cell therapy, what else do you think is on the horizon for this kind of treatment?

Dr. Chong:
I think there are many ways that we can try to ultimately increase efficacy for CAR T-cells, as well as really improve the safety profile. So, one way is to improve patient selection, so selecting which patients may benefit earlier. If patients are sicker, then they're more likely to have toxicity and we know that patients who are healthier tend to do better with CAR T-cells. And so, really selecting the right patients to be treated earlier may improve CAR T-cell outcomes.

There are also multiple different ways that we can try to modify the CAR T-cells to increase efficacy. And so just to name a few, for example here at Penn, we have an IL-18 secreting anti-CD19 CAR T-cell for patients, that is early first in human trial and that's really exciting. We're also trying to combine CAR T-cell therapies with other drugs. For instance, I'm conducting a trial looking at bispecific antibody in combination with CAR T-cells, to see if that can increase response rates. And so, these are just a few of the ways we can do that. Other ways are to, again, have multiple targets that the CAR T-cells can attack and another exciting, I think, approach is really to look at improving the composition of the product. Some of the research we've done here at Penn has found that the composition of the CAR T-cell product that's infused to the patients really is associated with efficacy, and so can we modify the types of cells we're infusing into the patient.

Dr. Turck:
Well, as our program comes to a close, I want to remind our audience that patients, family members and physicians may search clinicaltrials.gov to find information on trials being conducted in the US for relapsed or refractory follicular lymphoma. I also want to thank my guest, Dr. Elise Chong, for sharing her thoughts on CAR T-cell therapy, and its recent FDA approval for relapsed or refractory follicular lymphoma. Dr. Chong, it was great having you on the program.

Dr. Chong:
Thank you.

Announcer:
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