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CAR T-Cell Therapy for R/R Mantle Cell Lymphoma: Key Considerations

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 take a deep dive into CAR T-cell therapy for relapsed/refractory mantle cell lymphoma is Dr. Chenyu Lin. Dr. Lin is an Assistant Professor of Medicine at Duke University School of Medicine in Durham, North Carolina. Dr. Lin, thanks for being here today.

Dr. Lin:
Thanks for having me. Happy to be here.

Dr. Turck:
Well, to start us off, Dr. Lin, what are the CAR T-cell therapies approved for relapsed/refractory mantle cell lymphoma? And how do they differ from one another?

Dr. Lin:
There are currently two CAR T-cell therapies that are approved for relapsed/refractory mantle cell lymphoma. The first is called brexucabtagene autoleucel, or brexu-cel, and the second is lisocabtagene maraleucel, or liso-cel. And they have a couple similarities. The first is that both are autologous CAR T-cell products. That means that they depend on a patient's own native T-cells that get collected through apheresis and manufacture with the CAR. Both are also CD19-directed. That means that the chimeric antigen receptor is targeted against the CD19 antigen that's found on the surface of most B-cell lymphomas and B-cells in general. So those are the similarities.

They do differ in a few ways. Notably, they have different costimulatory domains, so brexu-cel has a CD28 costimulatory domain that's similar to another CAR T that many of us are familiar with called axicabtagene ciloleucel, or axi-cel, that's used for DLBCL. Car T-cell products with CD28 co-stim domains tend to have a faster initial T-cell proliferation and initial tumor elimination. And in contrast, liso-cel has a 4-1BB co-stim domain, so that's similar to something else on the market, tisagenlecleucel, which is just used for ALL and DLBCL. That 4-1BB co-stim domain is associated with greater CAR T-cell persistence. And clinically, we tend to see fewer severe CAR-associated side effects with that one.

Dr. Turck:
And what does the literature tell us about the efficacy of these therapies for this indication?

Dr. Lin:
I want to emphasize that there have been no head-to-head randomized clinical trials to tell us which CAR T is better, but here's what we do know, and this is all based on single-arm studies. So the use of brexu-cel for relapsed/refractory mantle cell lymphoma was studied in a single-arm clinical trial called ZUMA-2. So there were 74 patients, and in the intention-to-treat cohort in that study, they found an overall response rate of about 85 percent. And about 60 percent had a complete response.

We've had follow-up data since then, so there was a long-term follow-up study for ZUMA-2 where we saw that the median progression-free survival was about 26 months, so a little over 2 years, and overall survival was about 47 months, so just shy of 4 years. For the most part, we've since developed real-world data that's been generated. We've had an expanded access study called ZUMA-18; these have supported the clinical trial results. It's shown very similar outcomes, so I think that data's fairly reliable. Overall, the takeaway is

that brexu-cel has a fairly robust response rate, and some of those responses can be durable for these patients.

Liso-cel was studied as part of a mantle cell cohort in the TRANSCEND study. So there were about 104, I believe, patients with mantle cell who were apherese in that study. And liso-cel had an overall response rate of 83 percent and a complete response rate of 72 percent. The median progression-free survival in that study was about 15 months, and the overall survival by 18 months.

So I just gave you some numbers, right? And we may be tempted—certainly I'm tempted—to try to compare those numbers, and, on the surface, I might say, "Well, liso-cel looks like it has a higher response rate, but maybe the response isn't as durable as we have with brexu-cel." But I would be cautious about making comparisons between these different clinical trials.

Dr. Turck:
And how about their safety? Are there any common or major adverse effects or events that we should be aware of?

Dr. Lin:
Yeah. So there are definitely safety concerns with CAR T. It's considered a fairly intensive intervention. When I think about toxicities associated with CD19-directed CAR T, the ones that come to my mind immediately are cytokine release syndrome, or CRS, and immune factor cell-associated neurotoxicity syndrome, or we call that ICANS for short. And we know that we can manage these CAR T toxicities. We've gotten better at this over the years. With appropriate and timely intervention, we can really support our patients through these side effects and get them through it. There's rarely any fatal events with these.

When we think about the toxicities, we care about the higher-grade ones, so grade 3 or higher CRS or grade 3 or higher ICANS. Unfortunately, as I mentioned earlier, we don't have a comparative trial to look at what the rates of toxicity are for each of these products and compare it head-to-head. But what we do know is that in ZUMA-2, the rate of grade 3 or higher CRS was about 15 percent and the rate of grade 3 or higher ICANS was about 30 percent. So essentially, we have about 1/3 of patients who are getting pretty severe neurotoxicity with mental status changes when they get brexu-cel.

Liso-cel seems to be safer in TRANSCEND. The grade 3 or higher CRS was only about 1 percent, and the grade 3 or higher ICANS was only about 9 percent.

Dr. Turck:
For those just joining us, this is *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Chenyu Lin about the evolving landscape of CAR T-cell therapy and relapsed/refractory mantle cell lymphoma.

So now that we know a little bit more about the available CAR T-cell therapies, Dr. Lin, how can we select patients who may be appropriate candidates for this approach?

Dr. Lin:
Yeah, that's a difficult question. A good one, though. It's going to be a question that people will ask more and more now that we have two products to choose from. I will try to answer this question, acknowledging that there's not a lot of evidence here. Again, we have to remember that the approvals for brexu-cel and liso-cel were from single-arm studies, so we don't have randomized prospective head-to-head comparisons for this.

If it's rapidly progressive disease, we consider brexu-cel; we try to get them to CAR T quickly. If it's a frailer patient or an older patient, we may consider liso-cel instead. There are also special types of mantle cell lymphoma that historically have been challenging to manage with chemo. Some examples are TP53-mutated mantle cell or blastoid variant. Both of these are pretty aggressive. Fortunately, we do see responses to both CAR T products in these patients.

There's also mantle cell lymphoma with secondary CNS involvement, which is rare and difficult to treat. So when we look at the studies, the TRANSCEND study for liso-cel did include these patients with CNS disease, while ZUMA-2 did not. So I tend to prefer liso-cel for these patients with CNS involvement just because there's prospective evidence to support that. If you want to use brexu-cel, it's very reasonable. There's real-world evidence from CIBMTR databases that have shown that CNS response with brexu-cel, so it's fair if someone wants to choose that.

Logistically, there are some considerations. We hate to let that be a barrier, but sometimes we have to think about it. So every center does it differently, but typically at Duke, we'll monitor brexu-cel in the hospital for about 1 to 2 weeks, but for liso-cel, we can give it in the outpatient setting because it's relatively safer. So if the patient has a preference about being in the hospital or not or if institutional resources are limited, then that may make a difference in which product you pick.

All that said, if you have a patient, they're fit, they're able to tolerate intensive treatments, and if CAR T is indicated, then the most important thing is just to get them to CAR T. Both products have excellent responses, and they're both reasonable options for mantle cell

lymphoma.

Dr. Turck:
Would you tell us about the medication preparation process? And how it might impact when patients receive CAR T-cell therapy?

Dr. Lin:
Autologous CAR T-cell therapies are living drugs, and they require that we collect the T-cells from the patients themselves; we ship them off to the company for manufacturing, and then they isolate, they expand the T-cells, and they engineer the chimeric integer receptors onto the cells. And then these are sent back to us, and we can finally infuse those CAR T-cells into the patient. So it can take about 4 to 5 weeks, and unfortunately, not all of our patients have that kind of time to wait.

Dr. Turck:
So, Dr. Lin, from a bird's eye or global view, how have CAR T-cell therapies overall helped address the unmet needs of patients with relapsed/refractory mantle cell lymphoma?

Dr. Lin:
For mantle cell lymphoma, if we think about how we treat it, we usually treat it at the beginning with chemotherapy, an anti-CD20, monoclonal antibody, and/or a BTK inhibitor in some combination or sequence. Those are the earliest lines. When you get past those lines, that's when you run into more difficulty because you don't have as many options. So your options at that point are one: more chemo, which is often suboptimal; two: pirtobrutinib, which is a non-covalent BTK inhibitor; three is CAR-T; and four, in more desperate situations, an allogeneic stem cell transplantation.

So when we think about these options for relapsed/refractory mantle cell, pirtobrutinib is definitely a viable option, especially for older patients. The downside is that it is a longer-term therapy; you have to take it every day, and we don't expect that it'll be curative, so most often, I tend to use it for more indolent forms of lymph mantle cell lymphoma or those with lower tumor burden.

On the other end of the spectrum, we have allogeneic transplants, which is a one-time treatment; it has the potential for long-term remission just after one treatment, but it's also intensive. And we know that it has a lot of side effects, a lot of morbidity, and a good amount of mortality risk with it. So you only consider it for patients who are really fit, younger, who have already been through the other treatments, and they haven't worked. So then what you're left with is really CAR T.

CAR T, just like transplant, is a one-time treatment and has the potential for long-term durable remission. And while it does have more side effects than pirtobrutinib, or at least it's considered more intensive, it's certainly safer than a transplant. So in my mind, what CAR T offers for patients who are eligible is kind of a promising middle-ground approach that provides a nice balance of risks and benefits, a one-time, one-and-done, hopefully, treatment for certain patients.

Dr. Turck:
Well, with those considerations in mind, I want to thank my guest, Dr. Chenyu Lin, for joining me to provide his insights into CAR T-cell therapy for relapsed/refractory mantle cell lymphoma. Dr. Lin, it was great having you on the program.

Dr. Lin:
Nice to meet you. Thanks very much.

Announcer:
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