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Sequencing CAR T-Cell and Bispecific Antibody Therapies in Large B-Cell Lymphoma

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. Turck.

Dr. Turck:
This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Joining me today to discuss guidelines governing the sequencing of CAR T-cell and bispecific antibody therapies for patients with relapsed or refractory large B-cell lymphoma is Dr. Matthew Lunning. He's an Associate Professor in the Division of Hematology Oncology at the University of Nebraska Medical Center. Dr. Lunning, thanks for being here today.

Dr. Lunning:
Thank you, Dr. Turck. Great to here.

Dr. Turck:
So let's jump right into the National Comprehensive Cancer Network, or NCCN, guidelines, Dr. Lanning. They recommend CAR T-cell therapy as an option in the setting of relapse within 12 months of the most recent line of therapy. Would you tell us a little bit more about bridging therapy while waiting for CAR T-cell therapy?

Dr. Lunning:
Yeah, I really think that this is an area that was explored a little bit in the randomized trials that led to the approval of CAR T-cell therapy in the second line, especially in those patients who already either have primary refractory disease or those whose relapses occurred within one year. What lives outside of those trials is truly a period of time which I call not only the "pre-apheresis bridging therapy," but the "post-apheresis bridging therapy." We know that in clinical trials, patients were consented and then they were counted as part of an intent-to-treat population once they were apheresed. When you live in the commercial environment, patients will have a delay from actually being seen to when they can actually be apheresed, and so this creates a whole different population of what I call the "intent-to-CAR population," or also this "brain-to-vein time," which is the time that you want to do the CAR T-cell, the patient is on board, and we really want to go forward to when we can actually get them apheresed. And I think that this is a difficult period of time because sometimes it can take days, and sometimes it could take several weeks before you can get the apheresis. And we're really trying to tease out still the different variables in a patient's care that may allow us to see them on a Monday and apheresed them on a Friday versus see them on a Monday and 4 weeks later, we're still trying to get the apheresis slot based upon whether or not testing, insurance authorization, family dynamics, or logistics are all sorted out.

And so I think what's imperative in that time frame is to really understand the pace of the disease. You know, is it primary factoring progressing after initial therapy? Is this relapsing on a surveillance scan at three months where you caught the disease early, but the patient is asymptomatic? I think the data that we have right now in the pre-apheresis period of time is really showing that the therapy to try to avoid at almost all cost is a bendamustine-based therapy. We know that pola-BR is a regimen that has shown survival advantage over BR in and of itself. But I think that this lends to the NCCN guideline recommendation of Pola plus/minus rituximab, plus/minus benda. And I think in the pre-apheresis period of time, leaving the benda on the sidelines is incredibly important for T-cell fitness and the hopes of getting an in-specification product that comes back in the commercial environment. I really think as we start to see these real-world data sets continuing to emerge, hopefully what we'll start to see is really intent-at-CAR analyses.

Dr. Turck:
And would you walk us through some of the highlights of the clinical trial data demonstrating CAR T-cell's efficacy and safety benefits?

Dr. Lunning:
So in the first trial, which was the ZUMA-7 trial, axi-cell was randomized against second-line chemotherapy with a primary endpoint for event-free survival. And what was interesting in this trial is it met its primary endpoint and the EFS median was 8 months versus around two-and-a-half months in the control arm, which is chemoimmunotherapy and auto transplant, acknowledging that the biggest barrier to getting the transplant was the disease chemosensitivity. Right? So it wasn't like they were having toxicity. So it was kind of in keeping with what we would have expected in this high-risk population based upon other trials in the pre-CAR T-cell arena.

There was a second and a third trial, the BELINDA trial, which ended up being a negative trial with tisa-cel, which I believe was probably more so in regard to the clinical trial design. We could go on for another probably 10 minutes discussing that clinical trial design. But being that it was a negative trial and didn't lead to an approval, I'm going to jump to the third trial, which was the TRANSFORM trial. And this was a randomized trial of liso-cel versus chemoimmunotherapy. The differences here were you could get one cycle in the CAR T-cell arm for disease stabilization, and there was crossover allowed with regard to those patients that were on the experimental arm of chemotherapy. If they did have an event-free survival event, they could automatically jump into getting CAR T-cell as third-line therapy as part of the trial. Actually, these individuals were all apheresed, and some products were manufactured while others were stored, and they were only manufactured if an event-free survival event had occurred. So this trial did meet its primary endpoint of event-free survival with relatively similar numbers to the ZUMA-7 trial, especially in the control arm.

Dr. Turck:
Now turning to bispecific antibody therapy, the NCCN guidelines recommended only after at least two prior lines of systemic therapy. So what more could you tell us about that?

Dr. Lunning:
I think there are some subtle differences between glofitamab and epcoritamab. Glofitamab has a lead-in with a CD20 monoclonal antibody called obinutuzumab, followed by step-up dosing strategy. It is given intravenously, and it is a fixed-duration therapy. So if you go into an early CR and that CR is maintained, that bispecific can be put back up on the shelf and be pulled off the shelf if relapses were to occur. We saw some progression-free survival data at this last ASH meeting, which showed that if you can get into a CR, those CRs can be durable. I would caution if you're not in a CR, a PR, or stable disease, that disease is likely, if you stop therapy, only going to come back.

Now epcoritamab, on the other hand, is a subcutaneous injection. It still has a step-up dosing but does not have an antibody kind of lead-in. After it's step-up dosing—which is multiple weeks in a row once you get to the full dose—then it goes to every other week up until month 10, and then monthly thereafter. So this is a continuous dosing strategy, at least right now in large B-cell lymphoma. Again, I think CR is king. Both had about a 40 percent response rate, or CR rate overall. And what didn't trail too far behind was the CR rates in those patients that had previously received CAR T-cell. And so in my relapsed or refractory CAR T-cell population, I am choosing either glofitamab or epcoritamab.

Dr. Turck:
For those just joining us, this is *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Matthew Lunning about NCCN guidelines addressing the sequencing of CAR T-cell and bispecific antibody therapies in relapsed or refractory large B-cell lymphoma.

So now that we have a better understanding of these guidelines, Dr. Lunning, would you share an example of a real-world patient case that demonstrates how you would apply these principles in practice?

Dr. Lunning:
Yeah, I think that one of the things that we have really started to transition to is even in the frontline setting in large cell lymphoma, I think based upon the pola-X data with pola-R-CHP. In my practice, I think that was a practice-changing trial. But that does mean that we now have many more patients going forward that have been exposed to polatuzumab.

I am also starting to implement cell-free DNA technologies to not only look at my patients who are in a metabolic CR at the end of treatment, but also looking at their detectable minimal residual disease at the end of induction because that helps me lead into what I'm going to do. Because as I alluded to, 75 percent of the relapses or primary factory disease is going to happen in the first year. So if patients are in a metabolic CR but still have detectable minimal residual disease, you can be sure that I'm going to be seeing them very frequently and probably doing imaging on those patients in the first year. Because I think if they're going to relapse in the first year, what we're learning about CAR T-cell therapy is size matters. Right? The size of the tumor and the health of the patient, I believe, are directly

related to the odds of them going into a CR, and those CRs are durable CRs with cellular therapy. And so if you have detectable MRD and I catch a relapse early at low volume, I now have time where I don't have to tax the T-cells and I don't have to tax the body with potentially brain-to-vein apheresis bridging or post-apheresis vein-to-vein bridging. And I can get them to their CAR T-cell therapy with minimal disease bulk, and I think that that will translate to better outcomes in our CAR T-cell patients.

Dr. Turck:
And what advice would you give other healthcare professionals on treatment eligibility, timing, and adverse events when it comes to using these guidelines in practice?

Dr. Lunning:
Well, I think first off with regard to cellular therapy, we're realizing that age should not define eligibility for cellular therapy. I think we've struggled over time for whether or not age defines autologous transplant eligibility. I think that the pilot data in the second and third-line and beyond large B-cell lymphoma really opened our eyes to the ability to treat those individuals with comorbidities as well as those patients over the age of 70 with cellular therapy. I think that was doubled down by the recent publication of the ALYCANTE data looking at similar aged individuals with axi-cell.

So I wouldn't write off a patient in their 70s, 80s, or fit early 90s for potentially curative-intent cellular therapy. And just because they come for a CAR T-cell or a relapse refractory large B-cell lymphoma consultation does not mean that they're destined to get cellular therapy. I'm still going to discuss the other relevant agents in the space to find the best therapy that's right for them and their situation. I think that not everybody will go to CAR T-cell, and we now have much better options than we did 10 years ago.

Dr. Turck:
And lastly, Dr. Lunning, to bring this all together, would you review with us the impact you've seen on patient outcomes and quality of life when applying these guidelines in practice?

Dr. Lunning:
Yeah, I think with regards to some of the patient-related outcomes that have even come out of these randomized trials, there's a little bit of selection bias because those patients who don't do well with second-line chemotherapy likely don't go on and get to a transplant because of disease activity. But I think we have data now going years and years—even in third-line and second-line CAR T-cell now—of patients who have been able to have relapsed refractory large B-cell lymphoma go into remission and go on and have long-term disease-free survival. Granted, they do still probably bring back some memories if you had a cytokine release syndrome. And in fact, if you had neurotoxicity, it's not necessarily the patient that remembers neurotoxicity; it's the care team around them that remembers those dark days. We have gotten so much better at managing CRS and ICANS, which I think has translated to our ability to expand the treatment population in regards to cellular therapy. I think what we're going to try and figure out in the next 2 to 3 years is for the other therapies that are active, how do they go around and either make CAR T-cells work better or make there be less disease for the CAR T-cells to tackle, either on the front-end as a lead-in therapy or even on the back-end as part of maintenance strategies to try to suppress and get to the core last large cell lymphoma cell. And I don't think that we've even touched the surface of the potential of these therapies in our other indolent non-Hodgkin's lymphomas.

Dr. Turck:
Those are great points for us to consider as we come to the end of today's program. And I want to thank my guest, Dr. Matthew Lunning, for joining me to discuss sequencing CAR T-cell and bispecific antibody therapies in relapsed or refractory large B-cell lymphoma and applying related NCCN guidelines into practice. Dr. Lunning, it was great having you on the program.

Dr. Lunning:
Thank you, Dr. Turck. Have a great day.

Announcer:
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