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Debunking CAR T-Cell Myths: The Realities of Patient Selection, Safety, and Access

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:
Despite FDA approvals and growing clinical integration, CAR T-cell therapies remain clouded by misconceptions, some of which could impact patient outcomes. And that's why today, we're busting some of the most persistent myths and setting the record straight.

This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Joining me to discuss the realities of CAR T-cell therapy is Dr. Matthew Lunning, who's an Associate Professor in the Division of Hematology/Oncology at the University of Nebraska Medical Center. Dr. Lunning, welcome to the program.

Dr. Lunning:
Good day, Dr. Turck.

Dr. Turck:
Oh, likewise. To start us off, Dr. Lunning, from your perspective, what are the most common misconceptions clinicians still have about CAR T-cell therapy today?

Dr. Lunning:
Well, I think it is around who can get CAR T-cell. Is there an upper age limit that basically states because you're X-age, you cannot get CAR T-cell? I think there are still some comorbidities of interest that people think shouldn't be referred for CAR T-cell. And then often the disease status, so in what line of therapy should we be entertaining the idea of CAR T-cell?

Dr. Turck:
And just to follow up, how can misconceptions influence clinical decision-making and delay appropriate referrals?

Dr. Lunning:
Well, I think that if you look at the literature, only about 1 in 5 patients are getting access to their CAR T-cell therapy. That means that there are 4 out of 5 that are likely not even getting sent for CAR T-cell consultation. And again, that may be related to age. And I think we have numerous datasets now that show that in the CAR T-cell arena—both in that second-line high-risk population as well as in that population of two prior lines or more—there's really been no superiority or inferiority based upon age.

I will say that in the advanced age population, perhaps there may be a different safety signal and perhaps a higher risk of ICANS or neurotoxicity. But that still doesn't equate to a deficit or inferiority in efficacy. And so I think if we just start with age as the first barrier and then if you take age out of it, that then does open up the door.

Dr. Turck:
Now, when we talk about the ideal candidate for CAR T-cell therapy, how else do you determine whether the patient and the prospective treatment are a good fit?

Dr. Lunning:
If age is out the window, then you look at other comorbid conditions. And I think the pilot data really opened up the spectrum of patients that may be eligible for CAR T-cell. So in that trial, not only was age one of the variables—age greater than 70—but it also looked at

patients with an ejection fraction of 40 or greater. If you can look at the DLCO, which is not a common test done, at least in my pre-CAR T-cell workup, I believe it was 65 percent or greater. And one that's more relevant, I think, of all of those is creatinine clearance. I think that creatinine clearance greater than 30 was allowed in the pilot trial.

And so if you can get around the comorbidities of the patient, I think it does open up a broader population that could get access to CAR T-cell in the appropriate clinical setting, which, again, for CAR T-cells, now has a plethora of non-Hodgkin's lymphomas subtypes.

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. Matthew Lunning about common myths and realities centering around CAR T-cell therapy.

Now, if we switch gears a bit and focus a bit more on some of toxicities you mentioned, Dr. Lunning, there's cytokine release syndrome, or CRS, and immune effector cell-associated neurotoxicity syndrome, or ICANS, and those are both major concerns. So what should we be looking out for when treating patients with CAR T-cell therapy?

Dr. Lunning:
Well, I think that there are multiple CAR T-cell products that are in the commercial environment. There are many that are still going through the clinical trial experience, but I think we got a pretty good handle on CRS and ICANS as well as the timing. I think you have to revert back to some of the mechanisms of how the CAR T-cells are activated. And I think there's a discernible difference between those that have a co-stimulatory molecule called CD28 versus those that have a 4-1BB. And I think you can look at this as just two different cars with two different engines. Both are capable of going to 0 to 60 at a quick pace; it just may be and feel a little bit different.

In our practice, for those that are getting a CD28 co-stim, we are often giving prophylactic steroids at days 0, 1, and 2, a la ZUMA-1 Cohort 6 as well as ZUMA-24. Not necessarily to prevent CRS or the onset of CRS—I do think that it delays the onset of CRS—but the main reason is to prevent or decrease the risk of grade 3/4 ICANS. And I think that's why we give those prophylactic steroids in those patients who are getting CD8 co-stim CAR T-cells.

Now for those that are getting 4-1BB CAR T-cells, we often don't give prophylactic steroids, but we then utilize the time from infusion to onset of first CRS to really help guide us on whether or not we do active surveillance and symptomatic treatment with acetaminophen for grade 1 CRS. Or we may intervene early if the CRS event is seen within the first 72 hours of a 4-1BB CAR T-cell and potentially even give tocilizumab plus a dose of dexamethasone at 10 mg, again, not necessarily around the CRS significance, but more so about the downstream effects from that early CRS event that may predict higher-grade ICANS.

And I think that is the biggest barrier right now. And one of the things that we should be looking out for is, how do we reduce the risk of grade 3/4 ICANS? Because, in my opinion, that is where the excess length of stay lives. That is where the increased risk of infections comes from, and I think we have several datasets now that are showing that if you can decrease the amount of steroid burden in this patient population, then hopefully you can decrease the risk of long-term infection risk and perhaps even those prolonged cytopenias that may exist after day 29.

So I think it is incredibly important to think about and know that what you do in the first 72 hours may actually have some downstream impact to the success and the safety of the CAR T-cell.

Dr. Turck:
And given the prevalence of these adverse events, just for a historical perspective, how have management strategies evolved in recent years to better support patients through complications?

Dr. Lunning:
Well, I think we have so many CAR T-cells now on markets. Some of them are the same but go under different names, and some of them are the same in multiple different indications. And so I think it's been interesting to watch the onboarding of CAR T-cells in multiple spaces and try to customize around the engine: 4-1BB versus CD28 as well as the disease. Because while the engine may be different, the disease chassis that is supporting the car and the disease itself may also be a little bit different. So you may have more indolent diseases like follicular lymphoma where the pace of the disease may be slower. But if you're using a CAR T-cell that is a different engine, you may still use prophylactic steroids in that situation just to kind of stay consistent around your management plans. When you have so many different CAR T-cells for so many different indications and as you try to learn how to manage these patients more broadly, staying homogeneous in your management strategy can help you pick up trends in your care, even across disease landscapes.

Dr. Turck:
And as we wrap up our discussion today, Dr. Lunning, what's one takeaway you'd want every clinician to remember when considering CAR T-cell therapy for their patients?

Dr. Lunning:
It's that the access to CAR T-cell remains the biggest barrier to the success of CAR T-cell. I think that we have to be looking broadly at the CAR T-cell journey. This is a journey that often starts in the community at a center that does not have access or is not an authorized treatment center. And if you're having a question on whether or not the patient could get CAR T-cell, I think it is completely reasonable to pick up the phone and have that discussion because age doesn't discern or determine whether or not you're a CAR T-cell candidate. And even now, certain comorbidities may not declare a patient ineligible for CAR T-cell.

And I really want to put this out there that for those oncologists who don't have access to CAR T-cell, at least personally, I want you to be part of that journey. I want you to be part of that patient's care before CAR T-cell and after CAR T-cell so that it can be successful and increase the access to CAR T-cell by acknowledging that partnership. They're hopefully getting the CAR that can hopefully lead to either curative intent or long-term disease-free survival, depending upon the non-Hodgkin's lymphoma subtype for which the CAR is being employed. But also understanding that there may be some not only characteristic differences within the CAR T-cell that is used, but also the downstream percentage of toxicities and the day 29 and beyond management.

So I think that the field is rapidly evolving outside of clinical trials, and a lot of the data is living in the real-world experiences. But I think that the consultation and opening the door to more discussions around CAR T-cell access is really where the field has its best potential: to improve outcomes by getting more patients to be seen.

Dr. Turck:
Well, with those final comments in mind, I want to thank my guest, Dr. Matthew Lunning, for joining me to help separate myths from realities in CAR T-cell therapy. Dr. Lunning, it was great speaking with you today.

Dr. Lunning:
Thank you for the opportunity.

Announcer:
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