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Predictive Models for CAR T-Cell Therapy: Personalizing R/R LBCL Care

Announcer
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Dr. Turck:
This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Here with me today is Dr. Matthew Matasar, who's the Chief of the Division of Blood Disorders at Rutgers Cancer Institute and a Professor of Medicine at Rutgers Robert Wood Johnson Medical School. Together, we'll be discussing predictive models that can identify relapsed or refractory large B-cell lymphoma patients who are at risk of adverse effects from CAR T-cell therapy. Dr. Matasar, welcome to the program.

Dr. Matasar:
Dr. Turck, thanks for having me.

Dr. Turck:
Well, to start us off, Dr. Matasar, how are emerging models able to predict a patient's risk of relapse or progression?

Dr. Matasar:
So in terms of our approach to patients with newly diagnosed diffuse large B-cell lymphoma, certainly, we're talking about CAR T-cell therapy, which is available for a wide range of diseases: progressive lymphoma, adenolymphoma, plasma cell dyscrasias, you name it. But the most common scenario that they're used, at least in the lymphoma space, remains diffuse large B-cell lymphoma. And they're being used right now for patients with relapsed or refractory disease, either in the second-line or the third-line and beyond, depending on the patient populations and the time from relapse.

To get to a CAR T-cell therapy, the first step, unfortunately, is that of relapse. Being able to predict relapse following first-line therapy is certainly very important, both in terms of prognostication as well as in guiding decision-making. Right now, the very best test that we have that's clinically available is the end of treatment PET scan, where we know that patients who failed to achieve a PET-CR or a Deauville 1, 2, or 3 score are at very high risk for clinical relapse. And many such patients should go on to be biopsied to confirm a clinical suspicion of relapsing or refractory large cell lymphoma.

Certainly, there will be patients with a positive PET who do not have relapsed or refractory disease, and we would never advocate treating a patient on the basis of a PET scan without tissue confirmation. Unfortunately, there are those patients who achieve a PET CR who will go on to relapse subsequently. And we don't have great clinical tools at the ready to identify those patients. That may be changing. There are very provocative data that have been presented both at last year's and now this year's American Society of Hematology, or ASH conference, looking at novel approaches to detecting measurable or minimal residual disease, MRD.

And the currently commercially available assays are a little lacking in terms of positive and negative predictive value, limiting their utility in this situation. But there's a newer technology, not yet available, outside of the context of research which seems very promising called PhasED-Seq. It has a very powerful discriminating capability such that patients who are PhasED-Seq positive at the end of R-CHOP or R-CHOP-like therapy are at very high risk for early relapse.

And conversely, patients who have a negative PhasED-Seq assay following achieving CR1 have an extraordinarily favorable prognosis.

So we're starting to build studies around this test to say that for patients who are PhasED-Seq MRD positive at the end of treatment, we should do something for and with those patients rather than waiting for what may feel like an inevitable relapse.

Dr. Turck:

Now, if we zero in on how these predictive models are promoting the evolution of contemporary protocols, what kind of impact are they having on risk assessment?

Dr. Matasar:
So when we think about risk assessment around CAR T-cell therapy, they were more dialed in around a patient who's gone on, had a relapse, and is now approaching CAR T-cell therapy. And we can predict or prognosticate a little bit in terms of how that treatment's going to go in terms of safety, tolerability, and efficacy.

And there are a number of clinical models that we use in routine practice that can be informative for patients and for CAR-enabled physicians—the ones that are actually treating patients with CAR T-cell therapy—to help understand the risk of progression through CAR and also the risk of toxicities following CAR T-cell therapy.

And one model that's really become standard or at least commonly applied is the so-called CAR-HEMATOTOX score. And this is a very simple clinical algorithm. It takes five patient characteristics—baseline platelet count, baseline absolute neutrophil count, baseline hemoglobin, baseline ferritin, and the baseline CRP—and assigns a point for each of these, or up to two points, for ferritin or platelet count, based on how abnormal those labs are.

And patients who are CAR-HEMATOTOX low, who have no more than one point on the scoring system, are comparable to, and quite different from, patients who are CAR-HEMATOTOX high, meaning two or more points on the scoring system. And the CAR-HEMATOTOX score is able to tell us both: what the odds or likelihood are of experiencing significant early toxicity following CAR as well as a little bit about how likely CAR is to achieve durable benefit for a patient being treated for aggressive lymphoma.

Dr. Turck:
And is there anything else you can tell us about how these models can help with treatment planning?

Dr. Matasar:
Good question. So treatment planning for patients undergoing CAR can certainly be quite nuanced and quite complicated. There's a number of different choices that treating doctors have to weigh.

The first is which cellular therapy to use. And in the second-line setting for transplant-eligible patients, we have two approved agents: liso-cel and axi-cel. And then in the third-line and beyond setting, we have three approved agents: liso-cel, axi-cel, and tisa-cell. For second-line transplant ineligible, we only have one approved agent, that being liso-cell.

So choice of cellular therapy in that position is not as relevant as choosing whether or not to use cellular therapy versus alternative approaches if a patient may not be able to safely tolerate liso-cel. So these agents, these three different cells—axi-, liso-, and tisa-cell—all have different characteristics and a little bit different efficacy, and they can be quite different in terms of their toxicity profiles.

For a patient with underlying frailty, comorbidities can make you worried about their ability to tolerate cytokine release syndrome and ICANs. A high CAR-HEMATOTOX score may skew a physician towards choosing either liso-cel or tisa-cel depending on the scenario—cells that are associated with lower rates of high-grade ICANs and CRS as compared to axi-cel, which has higher rates of those toxicities. So it can help docs in terms of choosing which cell to potentially offer.

Another question around treatment planning is site of care. Many CAR T-cell centers, including mine, are able to administer CAR T-cell therapy to the majority of patients in an outpatient setting, for much or all of the course of care, with both lymphodepletion as well as CAR T infusion occurring in the clinic. And hospitalization is being limited to later in the course of care to manage toxicities or to increase level of supervision at periods of the greatest risk.

Patients who are at very high risk for early toxicity following CAR, as informed by CAR-HEMATOTOX or other models—that may lead both doctor and patient to prefer an inpatient treatment approach, where that very high risk of high-grade toxicity can be mitigated with, perhaps, earlier intervention in a hospital-based setting.

Dr. Turck:
With all this in mind, and you started to touch on this a little bit before, what have recent clinical studies found concerning the use of predictive models?

Dr. Matasar:
I think that we're learning, number one, that these models really do help. And given the complexities regarding coordination of care for CAR T-cell therapy, understanding the importance of looking at the decision-making process through the lens of safety and efficacy—as well as likelihoods of outcomes using models like CAR-HEMATOTOX—can really help inform a nuanced discussion between doctor, patient, and family caregivers around the personalized risks and rewards of pursuing such treatments.

We're also learning that these models may be useful outside of the land of CAR T-cell therapy alone. There are other T-cell-engaging treatments that are increasing in use both in lymphoma and other disease states, and now even solid tumor malignancies called bi-specific antibodies. And these work similarly to CAR T-cell therapy in terms of T-cell engagement, but they're bi-specific antibodies that bind onto a surface antigen on the malignant cell and an antigen on healthy T-cells, creating an immune synapse and allowing for T-cell expansion, activation, and T-cell mediated cancer-killing.

We're learning now that these same models that we've developed for patients undergoing CAR T-cell therapy may also have a role in informing the risks of bi-specific antibody therapy, such as cytokine release or infectious risks. And we reported at the recent ASH that you can use the CAR-HEMATOTOX model for patients undergoing one such treatment: a medicine called odronextamab in patients with aggressive or indolent B-cell lymphoma. And the CAR-HEMATOTOX score did accurately predict the risk of early infectious complications as well as, to a lesser degree, cytokine release syndrome following treatment with this bi-specific antibody. So these models tell us a little bit about the underlying immune context and the underlying risk of complications arising from T-cell activation, regardless of the mechanism by which that activation's occurring.

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 Matasar about how we can use predictive models to identify patients with relapsed or refractory large B-cell lymphoma who are at risk of adverse effects from CAR T-cell therapy.

So now that we have a better understanding of these predictive models, let's focus a little more on how we can apply them in clinical settings. Dr. Matasar, would you share some implementation strategies and related considerations with us?

Dr. Matasar:
So a lot of the challenge around CAR T-cell therapy, as we've been talking about, is how best to mitigate these acute risks, these acute toxicities. And approaching a patient receiving CAR-T through this lens gives the doctor and care team a real advantage because we have the ability to adjust our dials and think about how we can approach a patient in the context of their individualized risk to manage that.

And there's a number of different tools that we have available to us. We can change our premedication strategy. We've seen in a number of trials now that with increased attention to prophylaxis against cytokine release and ICANs, the neurological toxicities of T-cell engaging therapies, steroid prophylaxis can be a very powerful tool in trying to mitigate these risks, particularly in those patients at heightened risk as informed by models like CAR-HEMATOTOX.

So, we were initially quite leery of steroid prophylaxis, the worry being, well, steroids are going to kill the CARs, and now we've destroyed the very thing we've worked so hard to administer. And the data have accumulated over these last years. It's informing us that, no, steroid prophylaxis against toxicities is safe and does not lead to a decrement in effectiveness of the CAR-T cell therapy itself. So for patients who are at heightened risk for toxicities, steroid prophylaxis is the standard of care.

You can even go a step further here. We understand that there are patients who are going to be at risk for neurological consequences of ICANs, and that can be partially informed by CAR-HEMATOTOX and partially informed by other more routine clinical models, like baseline neurological status, baseline neurological toxicities, involvement of CNS structures, comorbid neurological illnesses, and the like.

And for patients who are at heightened risk for ICANs, particularly those that are receiving axi-cel, which is the CAR-T most clearly associated with neurological toxicity, there's evolving data coming from friends like Dr. Jay Park that you can add to the prophylactic regimen and medicine anakinra, which can, itself, further reduce the risk of ICANs. And taking these adapted, individualized, prophylactic strategies informed by individual patient risk is really the most sophisticated way we can approach the administration of CAR-T here in the modern era.

Dr. Turck:
And, in our last few moments here, Dr. Matasar, from a high-level view, how do you think predictive models can impact patient outcomes?

Dr. Matasar:
I really think that we need to be able to apply predictive models at the individual patient level so that doctors can, number one, inform patients and their families and caregivers of their individualized risks and benefits. And, number two, personalize treatment approaches in terms of cellular therapy choice, site of care, prophylactic regimen, and early intervention strategies to maximize the benefit from these treatments and minimize their toxicities.

Dr. Turck:
Well, given those potential impacts, I want to thank my guest, Dr. Matthew Matasar, for joining me to discuss the latest advances in predictive models for relapsed or refractory large B-cell lymphoma care. Dr. Matasar, it was great having you on the program.

Dr. Matasar:
Dr. Turck, thank you for the invitation.

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