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Mitigating CAR T-Cell Therapy AEs in R/R Diffuse 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. Brian McDonough.

Dr. McDonough:
This is *Project Oncology* on ReachMD. I'm Dr. Brian McDonough, and joining me to discuss strategies for mitigating and managing adverse events associated with CAR T-cell therapy in patients with relapsed or refractory diffuse large B-cell lymphoma, or RR DLBCL, are Drs. Matthew Matasar and Swetha Kambhampati. Dr. Matasar is the Chief of the Division of Blood Disorders at Rutgers Cancer Institute and a Professor of Medicine at Rutgers Robert Wood Johnson Medical School. Dr. Matasar, welcome to the program.

Dr. Matasar:
Thank you so much for having me today.

Dr. McDonough:
And Dr. Kambhampati is an Assistant Professor at the City of Hope Comprehensive Cancer Center. Dr. Kambhampati, it's great to have you with us.

Dr. Kambhampati:
Thank you so much for the invitation. It's a pleasure to be here and really looking forward to the conversation.

Dr. McDonough:
So recent clinical trials have shed new light on the safety profile of CAR T-cell therapies. Starting with you, Dr. Matasar, can you summarize the latest data on the incidence of key adverse events, such as cytokine release syndrome and neurotoxicity?

Dr. Matasar:
Of course. And we know that CRS, or cytokine release syndrome, and ICANS, or neurological syndromes associated with CAR T-cell therapy, are two of the key toxicities that we take into account when choosing CAR T-cell therapy and when educating our patients about the risks and benefits of such treatments. There are, of course, a number of approved CAR T agents, each of which has their own different profile in terms of likelihood of risk of these two key toxicities—CRS and ICANS—and the rates vary: CRS rates of 40 to 80 percent and ICANS rates of 20 to 50 percent depending on grading and severity across these different cellular therapies. But understanding that these are the two key toxicities is important to this practice.

We understand that not all patients are at equal risk of these events, and there are data from the French group and the modeling efforts to try to identify clinical and disease characteristics that may predict higher risks of CRS and ICANS, including the CAR-HEMATOTOX model, which identifies laboratory and clinical parameters that may put patients at higher risk for these two key adverse events.

Dr. McDonough:
And turning to you now, Dr. Kambhampati, can you describe your approach to managing cytokine release syndrome, or CRS, in patients receiving CAR T-cell therapy for RR DLBCL?

Dr. Kambhampati:
So management of CRS really depends on the grade and severity of CRS. And so Grade 1, which is mild CRS, is supportive in nature and consists of managing flu-like symptoms, myalgias, headaches, nausea, and fatigue. And then management of Grade 2 CRS involves management of hypotension, hypoxia, and mild signs of organ dysfunction with fluids, oxygen, and other supportive

interventions. And then Grade 3 CRS involves managing hypotension and moderate signs of organ dysfunction with vasopressor support or hypoxia with high-flow nasal cannula. Grade 4 CRS involves managing life-threatening complications, such as hypotension requiring multiple vasopressors and hypoxia requiring positive pressure or mechanical ventilation.

So tocilizumab is a humanized monoclonal antibody that blocks binding to IL-6 receptors and is FDA approved for the treatment of CRS. Tocilizumab can lead to rapid improvement and resolution of CRS symptoms in many cases, and tocilizumab can be ordered for Grade 2 CRS symptoms, such as hypoxia and hypotension that are not responding to supportive care interventions, such as fluid and oxygen. For severe Grade 3 or higher CRS symptoms or Grade 2 CRS that does not respond to tocilizumab, corticosteroids are usually prescribed in addition to tocilizumab.

Dr. McDonough:
So, Dr. Matasar, can you explain how you balance the need to manage these adverse events while preserving CAR T-cell efficacy?

Dr. Matasar:
When we were first embarking upon CAR T-cell therapy as a therapeutic intervention, there was at the time some very understandable reluctance to use medicines that could impact the health and persistence of CAR T-cells. There was an extreme reluctance to administer corticosteroids out of a concern that steroids, being lymphotoxic, could lead to loss of the CAR T product and thus loss of efficacy. We're increasingly understanding that this is not the case, and appropriate use of corticosteroids for patients, particularly those experiencing neurological syndromes like ICANS or refractory cytokine release syndrome, really do both require and benefit from steroids and that the use of steroids in this context does not jeopardize efficacy of the underlying treatment.

That being said, medicines like tocilizumab as a first-line intervention against cytokine release and anakinras as an adjunctive therapy will not impact the quality or efficacy of the CAR T-cell therapy. And using these earlier in the course of the evolution of adverse events can really abrogate the severity of CRS and ICANS and can really enhance patient outcomes without jeopardizing long-term efficacy.

Dr. McDonough:
For those just joining us, this is *Project Oncology* on ReachMD. I'm Dr. Brian McDonough, and I'm speaking with Drs. Matthew Matasar and Swetha Kambhampati about adverse events in patients with RR DLBCL.

So let's look at the role of the multidisciplinary care team. Dr. Kambhampati, how can they help treat and set expectations for patients and manage adverse events effectively?

Dr. Kambhampati:
Absolutely. I think CAR T-cell therapy is a very complicated and long treatment process that involves many phases, and each phase is associated with unique challenges. The CAR T-cell treatment journey encompasses initial consultation work-up, apheresis, bridging therapy if needed, lymphodepletion, CAR T-cell infusion, and toxicity monitoring and treatment, both in inpatient and outpatient settings. And the treatment involves many healthcare players, including physicians, advanced practitioners, nurse coordinators, nurse educators, apheresis nurses, inpatient and outpatient nurses, case managers, social workers, patient navigators, and many more. And so each player is very critical to the success of the CAR T-cell therapy, and each player plays an integral role in helping set expectations for patients and educating patients and caregivers early on in terms of what adverse events can occur and the time frame these adverse events can occur.

I think this education in terms of what to expect for CRS and neurotoxicity with CAR T-cell therapy as well as the other side effects is critical for patients and their caregivers and should be done early on, even with initial consultation and work-up and repeated throughout the visits.

Dr. McDonough:
And, Dr. Matasar, what advice would you give to care providers to ensure their patients are well-informed and supported throughout the treatment journey?

Dr. Matasar:
Honestly, patient education and care provider education is critical to the administration of a treatment as complex, nuanced, and with clear toxicities such as CAR T-cell therapy. Care providers are an important part of the care team; patients can't do this in isolation and don't do this in isolation. So teaching the providers about what to expect in terms of the best case scenario, the worst case scenario, and the most likely scenario, and teaching them what to watch for and what to understand in terms of the time scale of risk and the level of risk as well as educating them about what to do should adverse events occur, particularly for patients that are receiving outpatient CAR T-cell therapy is really important at layering additional support around a patient receiving this complex and potentially highly toxic

treatment.

Dr. McDonough:
Before we end today, Dr. Kambhampati, how can clinicians implement these strategies into practice to effectively monitor and manage the adverse events and provide optimal care?

Dr. Kambhampati:
There's a variety of strategies that clinicians can use to effectively administer CAR T-cell therapy and manage the side effects. I think the most important thing is for clinicians to work very closely with inpatient and outpatient nurses who are evaluating and charting regularly patient's vitals and their 10-point immune effector cell encephalopathy, or ICE, scores twice daily, so they can act early and quickly if any changes are observed. It's important for the clinician to thoroughly evaluate patients when there's any concern for CRS or ICANS, administer supportive care immediately, evaluate for infection in the presence of CRS and start antibiotics, use seizure prophylaxis for all patients, and obtain additional imaging with an MRI and possibly a lumbar puncture and EEG in the presence of ICANS.

I think there are many nuanced decisions as well that the clinician needs to make, and there are many factors that go into these decisions, such as which product to choose. There are three CAR T-cell therapy products available—axi-cel, liso-cel, and tiso-cel—and the decision of which to choose depends on the timing of apheresis and slot availability, patient disease characteristics and the patient's comorbidities and fitness. Whether to give bridging therapy or not and what exact bridging therapy to give is also a nuanced, complicated decision, and it depends on a patient's disease burden and prior lines of therapy.

And for all these reasons, patients can receive CAR T only in certain certified academic medical centers, given the complexity of the treatment, involvement of many healthcare persons, resources, and the experience and expertise required by the treating clinicians who are administering the therapy and managing the associated toxicity. So I think there are a variety of strategies that clinicians can use to optimize patient care for patients receiving CAR T-cell therapy.

Dr. McDonough:
With those takeaways in mind, I want to thank my guests, Drs. Matthew Matasar and Swetha Kambhampati, for sharing their insights on managing adverse events associated with CAR T-cell therapy in patients with RR DLBCL. Dr. Matasar and Dr. Kambhampati, it was great talking with you both and having you both on the program.

Dr. Matasar:
Thank you so much for having me today.

Dr. Kambhampati:
Thank you so much for having me here; it was a pleasure.

Announcer:
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