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Mastering CAR-T Cell Therapy in R/R Large B-Cell Lymphoma: Adverse Event Management

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 share strategies for managing adverse events related to CAR T-cell therapy in patients with relapsed or refractory large B-cell lymphoma are Drs. Caron Jacobson and Sairah Ahmed.

Not only is Dr. Jacobson the Medical Director of the Immune Effector Cell Therapy Program at Dana-Farber Cancer Institute in Boston, but she's also an Associate Professor of Medicine at Harvard Medical School. Dr. Jacobson, welcome to the program.

Dr. Jacobson:
Well, thanks so much for having me. I'm excited to be here.

Dr. Turck:
And Dr. Sairah Ahmed is an Associate Professor in the Department of Lymphoma and Myeloma Division of Cancer Medicine at the University of Texas MD Anderson Cancer Center in Houston. She's also the Director of the CAR-T program at MD Anderson. Dr. Ahmed, it's great to have you with us as well.

Dr. Ahmed:
Thank you so much for having me.

Dr. Turck:
Well, to start us off, Dr. Jacobson, would you give us an overview of the most common adverse events associated with CAR T-cell therapy?

Dr. Jacobson:
Of course. So CAR T-cell therapy is a unique therapy that involves the re-engineering of patients' own T-cells to be able to recognize their cancer cells and then hopefully launch an immune attack on those cancer cells. And so the side effects we see with CAR T-cell therapy are very different than what we see with other types of cancer therapies. They're largely related to that activation of the T-cells against the cancer cell, and so the side effects actually very much mimic our immune response against viruses like the flu. And if you think about how you feel when you have the flu, you often have fevers, body aches, muscle aches, fatigue, and headache, and those are not really due to the flu virus itself; it's due to your immune response against the flu virus. And those are very similar symptoms that you can experience within the first couple of days to the first week following CAR T-cell therapy. When that happens after CAR T-cell therapy, we call it cytokine-release syndrome, or CRS. And, again, it's the result of the activation of those T-cells that release inflammatory mediators into the bloodstream, called cytokines, which then recruit other inflammatory cells to further elaborate production of those inflammatory mediators.

And what the patient experiences is, at a minimum, flu-like illness, but we can't necessarily control how much inflammation the patient experiences. And if it gets beyond a certain level, patients can experience lowering of their blood pressure and difficulty breathing, and that can put stress on their heart, their lungs, their kidneys, or their liver in such a way that could require them to actually temporarily need to go to an ICU. Now, thankfully, that's very rare. This is a self-limited condition, and it's become even rarer as we've gotten better and better at managing these side-effects after CAR T-cell therapy because we've learned that we can intervene with our anti-

inflammatory drugs much earlier.

And the second side effect that we look for after CAR T-cell therapy usually happens towards the tail-end of that cytokine-release syndrome or even after it's resolved, and it's something that we call neurotoxicity. It also goes by another name: it's called the immune effector cell associated neurotoxicity syndrome, or ICANS. And so, again, this will usually happen somewhere between days five and 10 after CAR T-cell infusion. It's more common after CD19 CARs, which are the CARs that we generally use for diffuse large B-cell lymphoma. And it's not a definite that patients will experience this, but a good proportion of patients will.

The durability, or how long it lasts, is more variable than cytokine-release syndrome. For some patients it can last for a couple of weeks, and for others, it can last for a couple of days. And it's also very variable in terms of its intensity. So for some people, it can be mild confusion, and for other people, it can lead to a stupor and an inability to wake up and interact with the world. And so we monitor patients for this toxicity and intervene at differing intensities in order to try to prevent it from getting worse.

Dr. Turck:
Now, with that background in mind, let's turn to you now, Dr. Ahmed, and focus on the management of these toxicities. First, what signs might tip us off that a patient is experiencing neurotoxicity or cytokine release syndrome?

Dr. Ahmed:
Cytokine release syndrome is a term that we use as a composite for multiple symptoms. So patients have to have a fever as part of the definition for CRS, and then they can potentially have low blood pressure or a difficulty breathing with low oxygenation. And so we have to make sure that, number one, patients are treated for CRS in the time period they're receiving CAR T-cell therapy, but number two, that we also rule out other causes for those symptoms as they can also be evident for patients who have infection or sepsis or respiratory infections. And so we often will treat multiple things at the same time to make sure that we are covering for both CRS but also managing an underlying infection that we have not yet been able to identify with cultures.

The ICANs, or immune effector neurotoxicity, is also one that is a composite of multiple symptoms, and so patients can be confused, unable to remember where they are or what year it is. But they can also present with the inability to speak or stroke-like symptoms as well as seizures. So it's a multidisciplinary approach to both diagnose ICANs as well as to put into place the management.

For both of these particular side effects, there are specific treatments that are used for patients who are undergoing CAR T-cell therapy that are unique and not utilized for things like infection or stroke. But again, we want to make sure that we are trying to identify what we think is CAR-T-related toxicity as well as not ignoring what might be other things going on at the same time.

Dr. Turck:
And once we recognize those signs in a patient, Dr. Jacobson, how can we treat them?

Dr. Jacobson:
So I alluded to earlier, at least for cytokine-release syndrome, how our therapies are largely aimed at trying to turn off those inflammatory mediators from causing further inflammation. And so we do this largely in one of two different ways.

The first way is with an antibody to the IL-6 receptor, and IL-6 is one of those inflammatory mediators. This drug is called tocilizumab, and it's an IV drug that's given in a weight-based dosing. You can dose it every eight hours on four different occasions before we would consider someone not to be sufficiently responsive to tocilizumab. We would usually use tocilizumab if patients have prolonged low-grade cytokine-release syndrome or if their cytokine-release syndrome is associated with a drop in their blood pressure or with difficulty breathing.

The second drug we can use for a cytokine-release syndrome are corticosteroids, and we largely use dexamethasone. Again, for lower-grade toxicities that either don't respond to tocilizumab or where the physician thinks that patients need something in addition to tocilizumab, we can give this as a single 10 mg dose as needed. But for higher-grade toxicities, we would dose it more consistently, usually every six hours, until a patient improves to lower-grade cytokine-release syndrome.

When we see neurologic toxicity, drugs like tocilizumab don't work because they don't cross the blood-brain barrier. We do think that neurologic toxicity is related to some amount of inflammation that reaches the brain. And so we are really limited to using corticosteroids to treat neurologic toxicity because that is the one drug that can reach the brain where it can reverse some of the inflammatory stress within the central nervous system. We would usually employ it for neurologic toxicity that is starting to impair a patient's ability to perform their activities of daily living. So if they're getting to the point where they're so confused or incapacitated that they can't feed themselves or they don't know to get out of bed to go to the bathroom, we would definitely use corticosteroids in that case. And we certainly would be using them for patients who are having decreased responsiveness and decreased levels of alertness.

Dr. Turck:

For those just joining us, this is *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Caron Jacobson and Dr. Sairah Ahmed about the management of adverse events in patients with relapsed or refractory large B-cell lymphoma who are receiving CAR T-cell therapy.

So, now that we know how to identify and treat these toxicities, Dr. Ahmed, do you have any advice or best practices for integrating these strategies into practice?

Dr. Ahmed:
So the most important part of treating CRS and ICANs is first, identification, and then having algorithms in place wherein they can be treated quickly. Oftentimes, these toxicities happen within a certain timeframe after CAR T-cell therapy infusion, and sometimes, patients are treated outpatient, and sometimes, patients are treated in the hospital. The nurses are often the first point of contact, and so being able to have communication between nurses and the healthcare providers that are taking care of these patients, as well as having strategies to identify that these patients have received CAR T-cell therapy within the medical record, is key.

The best practices are also usually associated with the guidelines that are put out by the ASTCT—the American Society for Transplant and Cellular Therapy—which have white papers to help us better define the treatment at each grade and also escalate treatment and sometimes send patients to a higher level of care such as the ICU.

Dr. Turck:
And, if we come back to you, Dr. Jacobson, what role does education play in ensuring patient safety?

Dr. Jacobson:
This is a great question, and education is obviously vital not just for the clinicians who are taking care of the patients, but also for the caregivers for the patients—the friends and family who are at the bedside—and for the patient themselves. We obviously need to educate the nursing staff, the emergency room staff, the ICU staff, and all the physicians who take care of these patients in the hospital about the signs and symptoms of cytokine-release syndrome and neurologic toxicities so that they can be recognized early. And treatment decisions can be made, and treatments can be initiated in order to help prevent patients from getting sicker.

But we also need to educate the patient themselves so that they are aware of what to expect and then, more importantly, that the people who are sitting with the patient at the bedside, their caregivers, because the cytokine-release syndrome is one thing where both the caregiver and the patient will be aware that the patient's experiencing that. But if the patient experiences neurologic toxicity, usually it's much more distressing for the caregivers than it is for the patient because the patient often doesn't remember that period of their treatment plan.

And it's really important to warn the caregivers about the possibility of this toxicity and what it might look like and reassure them about its reversibility so that they can be more at ease at the bedside. It's also important to know that sometimes we do CAR T-cells as an outpatient. And in those instances, it's actually vital that the caregiver really knows about these toxicities and how to recognize them so that the patient can present to the clinic or to the hospital promptly should these side effects or toxicities emerge.

And then once the patient leaves the hospital because we think they've cleared their safety window, there is a small risk that these side effects could come back in the ensuing days to even one or two weeks. And so the caregiver needs be able to, again, recognize these side-effects if they were to recur in order to help the patient present promptly back to the clinic or to the hospital setting.

Dr. Turck:
Now, we certainly covered a lot today, so just to bring this all together before we close, Dr. Ahmed, would you tell us why the early recognition and management of adverse events is so important?

Dr. Ahmed:
So this is actually a really interesting part of the evolution of CAR T-cell therapy. If we look back at when commercial T-cell therapy was first approved in 2017, the guidelines in place were pretty closely identified with the pivotal clinical trials. And over time, as we've had more patients who receive CAR T-cell therapy and we are better aware of toxicity management, we have learned to be aggressive sooner and to potentially add in agents that we used to save for later grades of toxicity.

And there are now several publications that have demonstrated that we are much better at treating these toxicities and potentially even delaying or completely avoiding higher-grade CRS and ICANs. And so the early recognition and management of these adverse events have helped us to improve patient safety as well as decrease utilization of the hospital.

As you can see, there are a number of programs today that are very well-versed in delivering CAR T-cell therapy as an outpatient modality of treatment. And that's really because we are able to manage these patients much better over time with the toxicity

management algorithms that we have.

Dr. Turck:
Well, given that importance, I want to thank my guests, Drs. Caron Jacobson and Sairah Ahmed, for joining me to discuss how we can optimize patient safety in relapsed or refractory large B-cell lymphoma care. Dr. Jacobson, Dr. Ahmed, it was great having you both on the program.

Dr. Jacobson:
Well, thanks again for having me. This was fun.

Dr. Ahmed:
Thank you.

Announcer:
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