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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

What Are the Short-Term and Long-Term Toxicities With CAR T-cells?

Announcer:
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Dr. Raje:
My name is Noopur Raje. I will be talking to you about CAR T-cells both short-term as well as long-term toxicities. I think this is a really important discussion given that we have two CAR T-cell products available and considerations for these toxicity management is a shared approach with the treating physician as well as the CAR T-cell center, and therefore understanding these is critical.

So, I'm going to start out by talking about some of the acute toxicities, which are known with CAR T-cells. The first one being cytokine release syndrome. This, as you all know, is triggered by the activation of T-cells release of certain cytokines and chemokines, specifically IL-6 and IFN-gamma. Typically, the onset of this is within the first week. So, this is the kind of toxicity that we see when a patient is hospitalized, depending on the drug product, it can change. For example, with ide-cel, it happens more acutely within the first couple of days. With cilta-cel, we see a slightly more delayed cytokine release syndrome, typically happens a week into the CAR T-cell treatment. There are certain risk factors which are important for all of us to recognize, so that if you have a high disease burden or bulky disease and comorbidities the chances of CRS seems to be higher. Obviously, when a patient has been infused with the CAR T-cells, if they develop a fever, hypertension, hypoxia, or any evidence of organ toxicity, one has to be thinking of cytokine release syndrome and one needs to treat the CRS.

We have a way of grading CRS, and there's a way of managing CRS. The grading goes all the way from grade one through four. It's important to understand the majority of CRS that we see with the drug products, which are approved and available for multiple myeloma, including ide-cel and cilta-cel, we are mostly seeing grade one and two. And very little, if any, grade three and four toxicity. The management of CRS is largely supportive. You use antipyretics. You, actually, will do an infection workup and prophylactically treat patients with antibiotics. But the cornerstone for management of CRS is the use of the IL-6 receptor antibody Tocilizumab as well as the use of dexamethasone, which is a steroid, to quiet down this whole cytokine inflammatory response to the CAR T-cells.

Another really important toxicity which has been recognized in cell therapy in general is ICANS, or Immune Effector Cell-Associated Neurotoxicity Syndrome. This is triggered by passive diffusion of cytokines into the brain, trafficking of CAR T-cells into the CNS, and monocyte recruitment and macrophage activation. You can have kind of a biphasic response earlier after CRS. And, generally, you have to suspect ICANS when you see a decreased attention span, difficulty with language, impaired handwriting, confusion, agitation, or it can be extreme in the way of seizures and complete optimization. So, it could vary all along.

Again, like CRS, we are able to grade ICANS, all the way from grade one through grade four. And I've just highlighted the grading system on this table out here. Again, important to recognize that the CAR T-cell products that we have for multiple myeloma, including ide-cel and cilta-cel, we are seeing very little if any neurotoxicity at all. And, in fact, grade three and four neurotoxicity is extremely rare. Again, like CRS, the management of ICANS is supportive care. In essence, the difference here is you will use steroids before you use

Tocilizumab. And the other important thing to recognize is these patients need to be on seizure prophylaxis with Keppra. Should get neuro-oncology involved so that they can monitor these patients, because neurotoxicity can worsen if you do not treat adequately early on.

There are certain other CAR T-cell toxicities which are worth mentioning. One of them being cytopenias. Cytopenias, in general, resolved within the first one month, but there's a small subset of patients who can have prolonged cytopenias beyond two and three months. In essence, supportive care is the treatment of choice. Macrophage activation-like syndrome is a recognized syndrome with CAR T-cell therapies. It's usually seen in patients who have high disease burden to begin with, so you measure ferritin, IL-2 receptor, and coagulation factors. And one of the features which has really made a difference in the treatment of macrophage activation-like syndrome is the use of Anakinra early, before this progresses to something which is difficult to treat. Again, immunosuppression is common with the chemotherapy as well as with the CAR product. And given that we have our CAR products directed against BCMA, these patients will require IBIG supplementation as well as antibacterial prophylaxis.

I do want to mention a delayed neurotoxicity which has been seen with BCMA directed strategies. This is just one case report seen with cilta-cell where a patient was known to have a neurocognitive, hypokinetic movement disorder after a BCMA directed CAR T-cells. We do know that the caudate nucleus actually does express BCMA, so this, to me, is an on-target toxicity, but it needs to be recognized, needs to be treated early because otherwise, this can become progressive. Typically happens after that first one month anywhere between month one and month three post CAR T-cells.

Other CAR T-cell toxicities worth mentioning is infections. I've already talked about IVIg prophylaxis. I've already mentioned antimicrobial prophylaxis. These patients should be getting antiviral prophylaxis and sometimes PJP prophylaxis as well. What we are seeing is vital infections. So, thinking about parvovirus, CMV reactivation are all important factors, and you have to have a high index of suspicion for these toxicities. I do want to mention COVID since we are living through a pandemic as we speak. It's important that patients be vaccinated. It's difficult and it's a challenge whether or not they mount an antibody response and using a prophylactic strategy such as Evusheld is really important in this patient population.

So, again, for this section, my take-home points are understanding toxicities is critical, preempting them and trying to prevent or decreasing their incidence is really critical, using certain prophylactic strategies such as IVIg, treatment of infections. Infection prophylaxis is really helpful in mitigating some of these toxicities.

Announcer:
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