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

What Does the Design of a CAR T-cell Therapy Say About Its Efficacy and Toxicity Profile?

Announcer:
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Dr. Cohen:
Hello, my name is Adam Cohen from the University of Pennsylvania in Philadelphia, and today I'll be discussing the topic "What Does the Design of a CAR T-cell Therapy Say About Its Efficacy and Toxicity Profile?"

We know that there are a number of different components that go into making a CAR T-cell product. First, you have the source of the T-cells, which in all of the currently approved products, are autologous T-cells made from the patient, though allogeneic T-cells from healthy donors for off-the-shelf products are currently in development as well. Then, you have the different parts of the CAR construct itself, you have the binding domain, which in most products is derived from a single chain variable fragment. You have the hinge and trans-membrane domains. Then you have the costimulatory domains and the signaling domains. And if you look on the bottom right, you can see with the four currently approved CD19 directed CAR products, they all use the same antigen binding domain, but they have differences in their hinge and transmembrane regions, and differences in the costimulatory domains, CD28 versus 4-1BB. The different products may use different transduction methods, most use viral vectors, such as antivirus or gamma retrovirus, but there are other novel techniques such as transposons being explored. Each product has its own manufacturing method, which may have different ways they stimulate the T-cells and different cytokines they use and different lengths of manufacturing that can impact the quality of the final product, and then there may be differences in the lympho-depletion that's used between products and differences in the final dose that's administered. So, there's a lot of variability from product to product.

Now, one thing that may impact some of the the clinical outcomes is the costimulatory domains. This is something that's been explored most in the CD19 directed CAR T-cell products. At the top, you can see three trials using products that had a CD28 costimulatory domain. This is associated with perhaps more rapid initial burst of proliferation, more rapid initial growth, and less persistence, and you can see in these studies, there was perhaps a higher rate of CRS and neurotoxicity, higher proportion of patients needing Tocilizumab compared to the bottom trials, highlighted in the blue rectangle, which used 4-1BB, which is thought to perhaps have a little bit slower initial expansion, but greater memory formation and greater persistence. And in these studies, there was a little bit lower rates of CRS and neurotox. Interestingly, the efficacy, looking at these trials doesn't appear to be that different at least in DLBCL or ALL, with similar proportions of patients achieving long-term progression-free survival.

Now with the BCMA CAR T-cell products in myeloma, both ide-cel and cilta-cel use the same costimulatory domain, 4-1BB, but they do have different antigen binding domains. Ide-cel uses a mirroring derived SCFE that binds BCMA at a single site. Cilta-cel uses camelid or Llama-derived antigen binding domain that binds the BCMA at two different sites, thought to perhaps confer greater avidity, and uses two different heavy chain variable regions. And then there are even more novel binding domains being developed in myeloma. This is an example of one called CAR T-ddBCMA, uses a fully human synthetic binding domain, much smaller, thought to be perhaps less immunogenic, and that may lead to better persistence. And this is entered clinical studies as well.

And so one of the impact of the binding domains are that if they're not human, they can generate a host anti-CAR immune response, and that may impact the persistence, and so both with ide-cel and with cilta-cel, there's an initial burst of proliferation then gradual decline, and in both of these studies by six months or beyond, most patients did not have detectable levels of the CAR in their peripheral blood. And at least with the ide-cel study, we saw that that was associated with an increase in the frequency of patients who developed anti-drug antibodies. In this case, anti-CAR antibodies. What's unclear is how this immunogenicity and and persistence actually impacts outcomes and efficacy. And so there was still good durability of response in many patients, particularly with cilta-cel, even though the cell, the CARs may no longer be detected after six months. And so I think we need to really study this more and we await the ongoing studies with the less immunogenic, fully human binding domains to see if that improves persistence, and may improve better duration of response as well.

And looking at toxicities between these two products, the incidence of cytokine release syndrome is fairly similar between the two, as well as high grade cytokine release syndrome, which fortunately is only a minority of patients. What is different, however, is the timing of the onset of CRS. The median onset day is one in ide-cel, but it's seven days with cilta-cel, and this likely reflects more the lower dose that's used in cilta-cel, which is roughly tenfold lower compared to the highest dose of ide-cel, rather than any particular CAR design issues.

With neurotoxicity, 18% of ide-cel patients had any neurotoxicity. Most of these were were low grade. And again, the time to onset was rapid, day two median mimicking, or following the CRS onset. Cilta-cel had 21% of patients with any neurotox, perhaps a slightly higher rate of high grade neurotoxicity. This could be classic ICANS, which had a typical data onset of eight days, again, mirroring the CRS, but also several patients with other neurotoxicities with a later time to onset, median day 27, including the six patients who had the Parkinsonian-like movement and neurocognitive disorders. And it's unclear if this difference really reflects differences in patient populations versus something about the CAR construct or other features of the product itself at this time. The incidence of this other neurotoxicity has gone down in subsequent central cilta-cel studies, when the tumor burden has been better controlled going into infusion.

So the take home points, that multiple variables can distinguish each CAR T-cell product, not just the CAR design itself, the costimulatory domains may impact initial toxicity rates, at least with the CD19 directed CARs lymphoma. For the BCMA directed CAR products that are currently approved, they use the same costimulatory domain, but do have different binding domains and manufacturing techniques, that the impact on clinical outcomes remains unclear. One key difference though, is that there are differences in the timing of CRS onset may be related to the lower dose of cilta-cel, and this is something to keep in mind as you're treating these patients. With that, I'll stop and thank you for your attention.

Announcer:
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