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CAR T-cell Therapy What Information Do I Need To Provide to the Patients and Caregivers?

Announcer:
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Dr. Raje:
Hello. My name is Noopur Raje and I work at the MGH Cancer Center in Boston. We're excited that we have CAR T-cells available to our patients, but with that, I think it's important that we provide information, not just to the patients, to the caregivers as well, given that this is a team effort.

So, what should patients know about CAR T-cells? Well, I think it's important that we educate patients about what are CARs? What is the actual process of going through CAR T-cell therapy? What are the toxicities associated with CAR T-cell therapy? And what are the other options that patients should be considering knowing that CAR T-cells are not the only treatment option?

So, I think it's really important for patients to understand what the patient journey looks like when it comes to CAR T-cell therapy because it does require a lot of coordination. After we identify a patient who is eligible for CAR T-cell, typically after they've relapsed after a couple of lines of treatment, and they've received both immunomodulatory drugs, proteasome inhibitors, and CD38 monoclonal antibodies, those are the folks who are considered eligible. A patient has to go through an apheresis procedure. We collect the T-cells, give them to the manufacturer to then manufacture the CARs, and then about three or four weeks later, those CARs come back to us wherein we give them back to the patient after giving patients a little bit of chemotherapy.

This is what the process looks like. As I've already mentioned, you go through a leukapheresis. A central line is placed, the lymphocytes are collected. There's no growth factor to be given prior to this. Once these lymphocytes are collected, they're then sent to the company to actually create the CAR, and then four to five weeks later, these CARs are then injected back into a patient after a little bit of chemotherapy.

What we have available for multiple myeloma right now is CAR T-cells to a protein known as B Cell Maturation Antigen. This is a protein which is expressed on all multiple myeloma cells and other plasma cells as well but preferentially expressed on the multiple myeloma cells. And we know that BCMA actually helps with the proliferation and survival of multiple myeloma cells, therefore making it a really good cancer antigen target for immunotherapeutic strategies.

There are tons of different BCMA-targeted immunotherapeutic approaches; I've just highlighted some of them here. We're going to focus mostly on the BCMA CAR T-cells, but I think it's important for patients to know that there are other things like T-cell engagers, such as bispecific T-cell antibodies, as well as antibody-drug conjugates, such as Belantamab mafodotin for patients. So, what is a chimeric antigen receptor or CAR T-cell? Well, I've already talked about the fact that lymphocytes are collected from the patients. These lymphocytes are then genetically engineered. And what I mean by genetic engineering is the lymphocytes, we insert a CAR structure into the cell, as you can see out here. This CAR structure has an extracellular domain that is outside the cell and this is the domain that recognizes the BCMA that I've talked about. Internally, it has two other features in there. One of them is a CD3 zeta T-cell activation

domain and we also have a costimulatory domain. And in the context of myeloma, most of those costimulatory domains are 4-1BB and they allow for the expansion of the CAR T-cells once they're given to patients. We refer to these as second-generation CARs in the context of myeloma.

What are the other options? Well, I've already talked about bispecific T-cell engagers. And the way these work are, these are monoclonal antibodies which unlike CAR T-cells, these are off-the-shelf. What they do is have two arms to that antibody. One of the arms directed against the tumor cell, the other arm directed against the T-cells. As of right now, we have antibodies directed to certainly BCMA, which is the CAR T-cells are directed against, but there are several other targets such as Talquetamab and Cevostamab targeting other proteins present on myeloma cells. What these bispecific T-cell engagers do is target the tumor and then activate the T-cell, very similar to what is done by the CAR T-cells.

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 interferon-gamma. And 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 Iracell, it happens more acutely within the first couple of days. With Siltocell, 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.

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 early or 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 obtundation. So, it could vary all along.

And the take-home points, I think, is once you have relapse refractory disease I think it's absolutely critical that you think about CAR T-cells as an option because the data we have in terms of response and durability of response is quite remarkable, even in the relapse refractory state. It is also important to really discuss with your healthcare provider and your team to understand this CAR T-cell journey because it is a commitment when you decide to do CAR T-cells and you do need the support of your family members to be able to drive to the CAR T-cell center, live close by and get all of those logistics in place. So, with that, I thank you all for listening to this episode of patient information on CAR T-cells. Thank you.

Announcer:
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