Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/expert-answers-to-common-questions-for-improving-the-road-to-remission-with-car-t-cell-therapies-in-large-b-cell-lymphoma-considerations-for-community-practice/15570/

Released: 01/29/2024
Valid until: 01/28/2025
Time needed to complete: 15 Minutes

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

Expert Answers to Common Questions for Improving the Road to Remission with CAR T-Cell Therapies in Large B-Cell Lymphoma: Considerations for Community Practice

Announcer:
Welcome to CME on ReachMD. This activity, titled Expert Answers to Common Questions for Improving the Road to Remission with CAR T-Cell Therapies in Large B-Cell Lymphoma: Considerations for Community Practice is developed by AXIS Medical Education and is supported by an educational grant from Bristol-Myers Squibb Company.

Before starting this activity, please be sure to review the disclosure statements as well as the learning objectives.

Here's Dr. Caron Jacobson.

Dr. Jacobson:
Hello and welcome. I'm Dr. Caron Jacobson, Associate Professor of Medicine at Harvard Medical School and the Dana-Farber Cancer Institute. Today, I will be answering questions that were asked by clinicians during a recent educational series on CAR-T cell therapies in large B cell lymphoma. Our questions today will focus on three main topics: the first being patient and treatment selection, the second being outpatient CAR-T cell treatment, and the final topic will be monitoring and adverse events. So, let's begin.

So, the first topic we're going to talk about today is patient and treatment selection. A question we get asked frequently is: are there patients who are ineligible for CAR-T cell therapy? And more and more the answer to that question is no. Patients who would historically have been ineligible for autologous stem cell transplant are eligible for CAR-T cell therapy because patients can have less reserve in terms of baseline organ function and age, and still manage to get through CAR-T cell therapy successfully.

There's no centralized algorithm to determine whether patients are eligible for CAR-T cell therapy. Instead, every center will have their own eligibility criteria. But these are dynamic, and centers have been broadening those eligibility criteria since 2017 when CAR-T cells were first approved as we've gotten more and more comfortable with toxicity management and treating patients with baseline comorbidities. So, we do treat patients with baseline heart failure, pulmonary disease, renal failure, and there are some patients that we may meet and decide that the risk is ultimately too great. But that really has to be a decision at the CAR-T cell treatment center.

And so, I would encourage people to refer patients in. And they should be referred in as early as they possibly can. Generally speaking, I like to have patients referred into a line of therapy earlier than CAR-T cell therapy would be indicated. So, if we're talking about patients in the third-line, that would be when they need second-line treatment. And now that we have CAR-T cell approvals in the second-line, I would advocate for referring high-risk patients in at diagnosis or during their frontline chemoimmunotherapy in case they end up being primary refractory or early relapsing, or anyone who has sort of a slow response either on mid-treatment PET scans or sort of clinical assessment during their frontline chemoimmunotherapy.

There's no age cutoff for CAR-T cell therapy. And as I mentioned before, we are treating patients with kidney dysfunction, even patients on dialysis. It's actually the patients that have that creatinine clearance of 20 to 40 that I worry a little bit more about because it makes it hard to manage successfully with supportive care during cytokine release syndrome.

Another question we get asked is if patients do get bridging therapy and have a really tremendous, even complete response to bridging therapy, what do you do then in terms of their CAR-T cell therapy? And historically, we had been waiting for them to relapse in order to treat them. But there's more and more data to suggest that these patients may do very well getting CAR-T cell therapy with sort of a minimal disease state. And so, there are many centers that are treating patients at that point.

The last question that we get asked a lot is about equity both in terms of socioeconomic status, in terms of geographic distribution across the world, and specifically our country, and then also across areas of different racial diversity. And this is definitely an issue for CAR-T cell therapy because in very densely populated area, there are many CAR-T cell centers and patients don't have to travel very far to reach a CAR-T cell treatment center. But in large portions of our country, patients have to travel 200, 300, 400 miles in order to get to a CAR-T cell treatment center. And sometimes they come from places or occupations that don't allow them and their family to take a month off of work in order to get through the CAR-T cell treatment episode. And so, this is definitely an area that needs further improvement in terms of increasing access. And there's definitely a focus on trying to do that and trying to get more centers especially in not densely populated areas, up and running and to increase support and patient support for their CAR-T cell treatment episode.

The second topic we're going to talk about today is outpatient CAR-T cell treatment. So this is definitely something that is increasing in frequency and more and more centers are starting outpatient CAR-T cell programs. You might ask, what are the advantages to doing outpatient CAR-T cell treatment? So, for some centers, there is an economic advantage. There's better reimbursement patterns if patients can get their CAR-T cells out of the hospital, and actually stay out of the hospital for the first several days after that infusion. And for other centers the reimbursement doesn't necessarily matter if the patients are treated in the hospital or out of the hospital. But there are still some advantages to doing outpatient treatment. So, one is obviously bed availability. Our hospitals are crowded and so having patients who are not actually in the midst of their toxicities from CAR-T cells, but just waiting for them to start does tax the system. And so, keeping those beds open for patients who have medical issues that require hospital care is important.

I think the other is for patient satisfaction. I think many, many patients would prefer to stay in either a hotel room near the treating center or even in their home if they live nearby, and be able to come and go as they please, especially during the time period where they're not having toxicities. And so, for all of these reasons, there's an increased emphasis on trying to develop these outpatient CAR-T cell programs. Now these programs can either offer all of the CAR-T cell therapy as outpatient, or offer select products that are associated with either delayed or lower intensity side effects to select patients who are felt to be a decreased risk of developing these side effects.

And then how we bring these patients into the hospital also differs. There are some centers that are comfortable treating grade 1 CRS as an outpatient with close outpatient monitoring. And there are other centers that bring all the patients in at grade 1 CRS. That means probably sending patients through the emergency room, which requires quite a bit of education and handholding with the emergency room and ways to alert the emergency room that these patients are coming, because these patients obviously need to get managed and assessed quickly the same as someone who's coming in with chest pain or stroke-like symptoms.

I think another thing that really aids these programs is having centralized housing, even potentially with outpatient nursing services, which is something that I think the field has to develop. Certain centers have already done this, and others are moving towards that.

And then the last topic we're going to talk about today is monitoring and adverse events, which is a good jumping-off topic based on our last discussion about outpatient CAR-T cell therapies, specifically about how we manage these adverse events when they arise. And so obviously, the most immediate adverse events we see following CAR-T cell therapy relates to cytokine release syndrome and neurologic toxicity. One of the questions we get is, what is the mechanism of action of cytokine release syndrome? And it is T-cell activation upon reinfusion and seeing the tumor antigen. In the case of large B cell lymphoma, of course, that's CD19. This leads to the release of inflammatory cytokines, which then leads to activation of other immune effector cells like macrophages and monocytes and other lymphocytes, which then leads to further cytokine elaboration. And the end result of that is that patients can experience, at a minimum, flu-like symptoms with fevers and body aches and malaise and fatigue, but that can progress to leaky capillaries, which can lead to low blood pressure and fluid leaking into the lungs and hypoxemia. And then if that progresses to the point where patients require vasopressor support or intensive respiratory support they often may require an ICU. Thankfully, that's rare. It happens less than 10% of the time with all of the CAR-T cell products. But we do know that high-grade cytokine release syndrome happens more frequently with axicabtagene ciloleucel, or axi-cel, compared to liso-cel, or lisocabtagene maraleucel, or tisa-cel, or tisagenlecleucel and that has to do with what the costimulatory domain is with those three different CARs. It's CD28 with axi-cel, and it's 4-1BB with liso-cel and tisa-cel, which changes the pharmacokinetics of how the CAR-T cells expand and are activated upon reinfusion.

And the second toxicity we see is neurologic toxicity or immune effector cell-associated neurologic syndrome. And that toxicity happens towards the tail-end of cytokine release syndrome and is also more frequent and more often higher grade with axi-cel, compared to liso-cel or tisa-cel.

Now, that being said you might say, then why don't we treat almost uniformly all patients with the less toxic CAR-T cell therapy? And some of that has to do with the fact that although axi-cel has the highest-grade toxicities, it has the most reliable and quickest turnaround time for these CAR-T cells. And so, many of our patients have too much disease at the time that we collect their T cells, and we're worried about this, you know how quickly we can get them to CAR-T cells. And even though there is more toxicity with axi-cel we are very good at managing that toxicity and getting patients through it. And so, it becomes more important that we're able to get a product back and get the product into the patient and give them a chance to respond, than it is about - whether they might have more toxicity. And what that amounts to is that, generally for patients with really bad lymphomas, we're picking axi-cel, and then for patients with better-behaving lymphomas, but who maybe have more comorbidities or are of older age, they tend to get liso-cel, and less frequently tisa-cel.

There was a cohort on one of the axi-cel studies that did give prophylactic dexamethasone: a dose on day 0 of the CAR-T cell infusion, a dose the day after, and a dose the day after that as a preventative measure to try to decrease the rates of grade 3 CRS and grade 3 neurologic toxicity. And they did do that; they cut those rates by about 50%. And it didn't seem to impact efficacy, although it was a relatively small cohort. And so, I wouldn't say there's been uniform adoption of prophylactic dexamethasone but if you are taking somebody into CAR-T cell therapy who maybe has borderline organ function or borderline performance status or very high pretreatment inflammatory markers, those may be patients that we're worried about, in terms of both having higher-grade toxicity, as well as maybe not being able to tolerate it as well. And so, those may be patients that we do choose to use prophylactic dexamethasone.

So, there are some side effects that can happen later after that initial sort of first 2 to 4 weeks where patients are at risk of CRS and neurologic toxicity. And these include things related to the immune suppression of CAR-T cells. So, we know that CD19 CARs have an on-target off-tumor effect on normal healthy B cells, causing B cell aplasia. Lymphodepletion also leads to T cell lymphopenia for quite a while after CAR-T cell infusion; it can even be up to 12 to 18 months. And then about a quarter of patients will have prolonged cytopenias, which means that they have cytopenias that last beyond day 30 is often with neutropenia and thrombocytopenia. And we don't know exactly why that is, but we do believe it's an immunologic phenomenon that usually can get better within 3 to 6 months after CAR-T cell infusion.

And so, we need to think about how to manage these patients both preventatively as well as how to survey them for opportunistic infections. And so, we do keep patients on prophylactic herpes virus prophylaxis, usually with acyclovir, and PJP prophylaxis usually with Bactrim for at least 6 months, and only stop those when their CD4 count is over 200. We also monitor IgG levels and tend to replete them especially in patients with frequent infections if they fall below 400.

There were questions about fungal prophylaxis and CMV monitoring. And our infectious disease doctors actually looked at all of our patients, even the ones with prolonged cytopenias to track the incidence of fungal infections in our patients, and they were quite low. They ultimately concluded that fungal prophylaxis was not necessary, even for patients with prolonged neutropenia. But we do know that CMV reactivation can be a problem for some of our patients, especially patients who got protracted steroids to treat toxicities while they were in their acute post-monitoring period. And so, our rule of thumb is if someone has had more than 5 doses of dexamethasone at 10 mg or higher we usually do weekly CMV monitoring as well as fungal monitoring for at least the first month following CAR-T cell infusion.

So, this has been a great opportunity to answer clinician's questions about CAR-T cell therapy for the treatment of large B cell lymphoma. I'd like to wrap up by providing a few take-home messages.

I think the most important thing to take away from these questions and the responses to these questions is that there's almost no patient who's automatically ineligible for CAR-T cell therapy these days. We really do encourage patients to be referred if they meet the label for CAR-T cells at this point, and let the CAR-T cell treatment center decide on eligibility. So, there may be patients that are a little bit too borderline and may not be able to move forward. And there may be patients who opt not to move forward because of a discussion about the toxicities or the logistics of CAR-T cells. But every patient should get that chance.

And so, I would encourage patients to be referred. And early referrals absolutely is the best way to both maximize efficacy and minimize toxicity. And so again, I recommend referral one line of therapy before the CAR-T cell therapy is needed so the patient is already plugged in and known to the CAR-T cell treatment center. So again, if that is in the third-line we would recommend when salvage chemotherapy is being started, to refer that patient into the CAR-T cell treatment center. And if we're thinking that the patient might end up being a second-line candidate because they are likely to be early refractory, or to be primary refractory or early relapsing, we would encourage referral during the initial frontline treatment phase.

And then finally, the logistics of CAR-T cells because of the toxicities we see and the need to be close to a CAR-T cell treatment center

still creates an issue for access for a good proportion of patients across the United States and the globe and this is definitely something that needs attention and further resources to support.

So, we just had our annual ASH meeting in San Diego and there wasn't a ton of new data related to CAR-T cell therapy for lymphoma. But there was a lot of real-world data to support the use of CAR-T cell therapy in broader patient populations. So once again, as we use these products in more and more patients, many of whom would not have been eligible for the pivotal clinical trials we see that the efficacy is maintained, and the toxicity is actually improving over time.

An interesting study is the ZUMA-12 study which actually looked at axi-cel in frontline large B cell lymphoma and is actually the steppingstone for a current randomized frontline study of axi-cel versus standard of care for high-risk frontline large B cell lymphoma. We saw a 3-year update on that data which showed that 75% of patients who received axi-cel after two cycles of R-CHOP-like chemotherapy with high-risk disease, meaning IPI 3, 4, or 5, or double-hit lymphomas actually were alive and maintaining their response at that 3-year time point, which is very exciting and tells us that we may not have reached the limit of where we can use CAR-T cell therapy in large B cell lymphoma.

So, with that, we'll end today's session. I want to thank our audience for listening and goodbye.

Announcer:
You have been listening to CME on ReachMD. This activity is provided by AXIS Medical Education and is supported by an educational grant from Bristol-Myers Squibb Company.

To receive your free CME credit, or to download this activity, go to reachmd.com/CME. Thank you for listening.