

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Advances in CAR T-Cell Therapy for Chronic Lymphocytic Leukemia



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H&O How does CAR T-cell therapy work?

DP A patient's T cells are removed through leukapheresis and then genetically modified in the laboratory so that they express a chimeric antigen receptor (CAR). The most common method used to introduce the new gene is through viral transfection, either with a retrovirus or a lentivirus. The new gene is integrated into the genome. It is transcribed and translated. The new receptor on the T cell can now recognize a target antigen. The CAR has a targeting domain, which is typically a single-chain variable fragment of an antibody that can target an antigen on a tumor cell. The most commonly targeted antigen is CD19, which is found on most B-cell malignancies. Internally, the chimeric molecule has a signaling domain, which will signal the T cell to become activated to divide, proliferate, and kill its target cells. The T cell can now kill the CD19-positive cell. The T cells can also undergo massive proliferation in vivo, magnifying the anti-tumor response. Notably, the CAR molecule provides not just proliferation signals, but also survival signals to the T cell. All the CARs have a stimulatory domain, usually a CD3 zeta chain, and a costimulatory domain. In most cases, costimulation is provided by either CD28 or 41BB (CD137).

H&O Which CAR T-cell therapies are approved by the FDA?

DP Two CAR T-cell therapies have been approved by the US Food and Drug Administration (FDA). Tisagenlecleucel (Kymriah, Novartis) is an anti-CD19 CAR that has a

costimulatory domain of 41BB (CD137). It is approved for the treatment of acute lymphoblastic leukemia (ALL) in children and young adults (≤ 25 years).

Axicabtagene ciloleucel (Yescarta, Kite Pharma) also targets CD19, but it uses a CD28 costimulatory domain. It is approved for adult patients with relapsed/refractory large B-cell lymphoma. The indications are

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diffuse large B-cell lymphoma, transformed follicular lymphoma, primary mediastinal large B-cell lymphoma, and high-grade B-cell lymphoma.

H&O What data led to the approval of these agents?

DP The approval of tisagenlecleucel was based on a large international trial of 63 pediatric patients with relapsed/refractory ALL. Nearly all of these patients have no other effective treatment options. In the trial of tisagenlecleucel, a complete remission occurred in more than 80% of patients, which is unprecedented for relapsed/refractory ALL. The CAR T cells were prepared via central manufacturing.

Approval of axicabtagene ciloleucel was based on results from a large, multicenter trial of more than 100 patients with relapsed/refractory non-Hodgkin lymphoma. The objective response rate was more than 80%, and the complete response rate was more than 50%. Axicabtagene ciloleucel is approved for adult patients with relapsed or refractory large B-cell lymphoma who have received 2 or more lines of systemic therapy.

In both of these studies, there were significant relapse rates. However, many of the patients in these studies have remained in remission for several years.

H&O Could you please describe your research in CAR T-cell therapy and CLL?

DP At the University of Pennsylvania, we have been studying CAR T-cell therapy in chronic lymphocytic leukemia (CLL) for more than 7 years. We developed tisagenlecleucel, and treated the first patients in 2010. We have shown that CAR T-cell therapy can be dramatically effective for many patients with relapsed/refractory CLL who have run out of effective treatment options. The first 2 patients that we treated remain in remission more than 7 years later, with no detectable evidence of CLL by any measure. In some patients, the CAR T cells eradicated 7 and a half pounds of tumor. When CAR T-cell therapy works, the results can be dramatic. Unfortunately, it does not work often enough. Just over 50% of CLL patients respond, and between 25% and 35% of patients achieve a complete remission. Among these patients, the relapse rate is low. We have been focusing research on trying to understand why CAR T-cell therapy works well in some patients but not others, in an effort to predict which patients are most likely to benefit.

This research has led to a study that is combining CAR T cells with ibrutinib (Imbruvica, Pharmacyclics/Janssen), an effective therapy for CLL. Our group has data suggesting that ibrutinib might make the CAR T cells more functional and more active against CLL. Ibrutinib might make the CLL cells a better target for the CAR T cells. We are finishing a clinical trial evaluating CAR T-cell therapy in patients who are receiving ibrutinib, but still have active disease. Some preliminary data have been presented at various meetings. We are optimistic about the exciting results seen with this combined approach.

H&O What are the adverse events seen with CAR T-cell therapy?

DP The most unique adverse events are cytokine release syndrome and neurologic toxicity. Cytokine release syndrome occurs with rapid T-cell proliferation and immune stimulation. Most patients who respond to

CAR T-cell therapy develop some degree of cytokine release syndrome. It can be mild to severe. It is similar to a severe flu-like syndrome, and usually starts with a low-grade fever that escalates. Fevers can be high, reaching more than 105°F. Cytokine release syndrome can be associated with anorexia, nausea, vomiting, and diarrhea. As it evolves, it can lead to capillary leak syndrome with pulmonary edema and hypoxia, as well as life-threatening hypotension.

Interleukin 6 (IL-6) is probably a central driver of cytokine release syndrome. Along with supportive care, fluid resuscitation, and oxygen, the anti-IL6 antibody tocilizumab (Actemra, Genentech) has been remarkably effective for most patients with cytokine release syndrome. Fevers will resolve within a few hours. Patients who are hypotensive will have normalization of their blood pressure. Their oxygen requirements will start to improve. Tocilizumab has become the mainstay of treatment for patients with severe cytokine release syndrome.

The neurologic toxicity is less understood. It can lead to confusion, delirium, aphasia, seizures, and even cerebral edema, which has been lethal in some cases. The cause of neurologic toxicity is unclear; it does not seem to be directly related to IL-6. It can develop during cytokine release syndrome or after the syndrome resolves. It does not quickly respond to tocilizumab or anticytokine therapy. In most cases, with supportive care, neurologic toxicity resolves spontaneously after a few days or up to a couple of weeks. More severe cases are managed with corticosteroids, although the efficacy of this approach is uncertain.

H&O How does CAR T-cell therapy compare with other treatments for CLL?

DP It is difficult to compare CAR T-cell therapy with other treatments. It has been used primarily in patients with multiply relapsed or refractory disease, and there are not many treatments for CLL in that category. In contrast to other treatments in CLL, CAR T-cell therapy is a one-time treatment. Repeated dosings are not required. When CAR T cells are effective, they can induce deep clinical remissions even as assessed by deep sequencing, which can detect 1 in 1,000,000 CLL cells. Few treatments for CLL can induce deep sustained complete remissions.

H&O What are you learning about CAR T-cell therapy?

DP We are beginning to understand when CAR T-cell therapy may be effective. We are learning more about proper dosing and how to schedule the doses. CAR T cells can proliferate to remarkably high levels, ranging from a

thousandfold to ten-thousand-fold. They can persist in the body for several years. In some patients, they have persisted beyond 5 years and remain functional. We have learned, in some cases, how to predict side effects. We have learned what induces cytokine release syndrome and how to manage it. The field continues to rapidly evolve.

H&O Do you anticipate that the production of CAR T-cell therapy will become easier in the future?

DP It is already easier now, and the field is moving rapidly. Research is evaluating how to accelerate production time, how to make the cells more potent, how to define the optimal graft, and what the best cell product would be. Overall, we can anticipate easier, faster production of CAR T cells over time.

H&O What do you tell your patients about treatment with CAR T-cell therapy?

DP I explain why CAR T cells may be a reasonable option, and how often this treatment is effective. I explain the process of production. I also review the potential side effects in detail. I explain the cytokine release syndrome, how it may manifest, and the possible interventions. Many of the side effects do not occur immediately, but can be seen up to 3 weeks after the infusion. The adverse events require unique expertise to manage, so we ask patients to stay near our center for about 4 weeks after administration of CAR T-cell therapy for treatment by a specialized group of clinicians.

H&O Is there any other promising research in CAR T-cell therapy?

DP Enormous progress is being made. The use of CAR T cells targeting CD19 has been dramatically effective.

Research is now trying to identify other targets for different malignancies.

Researchers are trying to develop CAR T cells that can be controlled, perhaps by having suicide signals that allow them to be killed if needed. More exciting is research trying to regulate them—turn them on, off, up, and down at will biologically. That knowledge should improve safety.

Research is moving quickly to combine CAR T cells with other therapies. As I mentioned, we are studying CAR T cells in combination with ibrutinib. This approach appears to enhance the CAR T-cell effect in clinical trials of CLL. Other studies are evaluating whether checkpoint inhibitors can increase activation of CAR T cells. A great deal is being done in this rapidly evolving field.

Disclosure

Dr Porter has received research support from Novartis, and holds patents and intellectual property interest related to anti-CD19 CAR T-cell technology licensed by the University of Pennsylvania to Novartis.

Suggested Readings

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