CAR T-Cell Therapy and the Pharmacology of Managing Cytokine Release Syndrome

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Presenters' disclosures of conflicts of interest are found at the end of this article.

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In just over a decade, chimeric antigen receptor (CAR) T-cell therapy has gone from basic science to the American Society of Clinical Oncology's "2018 Advance of the Year," helping heavily pretreated patients with poor prognosis achieve durable remissions. While there are currently two CAR T-cell therapies approved by the US Food and Drug Administration (FDA) for acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma, there are also hundreds of clinical trials underway.

At JADPRO Live 2018 in Hollywood, Florida, Jae Park, MD, an assistant attending physician at Memorial Sloan Kettering Cancer Center in New York shared background and clinical information regarding CAR T-cell therapy in ALL and large-cell lymphoma and highlighted how to identify patients who meet criteria as candidates for treatment. Amber King, PharmD, BCOP, a leukemia clinical pharmacy specialist at Memorial Sloan Kettering Cancer Center, discussed strategies to mitigate cytokine release syndrome and other serious side effects of CAR T-cell therapy in concordance with Risk Evaluation Mitigation Strategies requirements.

CAR T-CELL DESIGN AND MANUFACTURING

As Dr. Park explained, a CAR T cell is the combination of an antibody and a T-cell receptor that offers the advantage of both—the specificity of antibody target recognition and the effector mechanisms of T cells. Once the CAR is constructed, it is inserted into a T cell that comes from either the patient (most common) or other alginate donors using either a retrovirus or lentivirus. This process—from T-cell extraction to cellular manufacturing—can take between 7 and 14 days. Once these cells are made, they can either be infused fresh or, more commonly, cryopreserved and shipped to the clinic before being thawed and infused back into the patient.

Even though the manufacturing process takes between 7 and 14 days, said Dr. Park, with precollection and quality control included, this can extend to 4 or 5 weeks, which must be factored into patient selection.

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"The right patient is able to survive at least through the process of a four-week period of time to receive the T cells," he said.

Although patients are able to receive chemotherapy or any therapy to stabilize their disease during the manufacturing process, some patients are refractory to all the lines of therapy. Patients who are out of options to control their disease may not be the best patients to be treated with CAR T cells, Dr. Park observed.

For those who can survive the wait, however, CAR T cells offer several advantages. There is universal application due to human leukocyte antigen–independent antigen recognition, and because the T cells come from the patients themselves, there is minimal risk of graft-vs.-host disease, such as that with allogeneic stem cell transplant. More importantly, however, because it is a living drug, said Dr. Park, CAR T-cell therapy offers the potential for lasting immunity with only a single infusion.

CLINICAL DEVELOPMENT

As Dr. Park reported, CAR T-cell therapy was first used to treat patients with chronic lymphocytic leukemia (CLL) in 2007. Over the past decade, the technology has been used to target the CD19 molecule in several other B-cell malignancies, including B-cell lymphomas and ALL. More recently, with second-generation CAR T cells, researchers at Memorial Sloan Kettering have added a CD28 costimulatory domain to increase the durability of response and enhance clinical outcomes.

A phase I trial of 19-28z CAR T cells in relapsed/refractory ALL demonstrated a complete response rate of 85%, said Dr. Park, which is significantly higher than the 20% expected response rate from conventional chemotherapy alone (Park et al., 2018). Furthermore, these outcomes have been replicated across a myriad of different CAR T-cell trials in ALL.

"The 80% complete response rate is what generated the initial excitement for CAR T-cell therapy several years ago and showed the true potential of the treatment," he explained. "Most of these patients had at least three or four prior lines of therapy, meaning they were very refractory to conventional treatment, but these results showed CAR T-cell therapy could be a very encouraging therapeutic option."

Survival outcomes, however, were not as good as initially hoped. At median follow-up of 29 months, median overall survival is 12.9 months, said Dr. Park, suggesting there is still room for improvement with this technology.

"Despite the initial 80% complete response rate, early relapses do happen, so we need to observe these patients very carefully," he added. "It's really too early to celebrate until about 6 months after infusion, but for patients who make it that far without relapsing, the chance of relapse after that is significantly lower."

Even though there are early relapses, some patients do experience long-lasting responses beyond 5 years. When the "dismal prognosis" of these patients prior to CAR T-cell therapy is considered, said Dr. Park, the excitement generated by the treatment is understandable.

PREDICTORS OF LONG-TERM RESPONSE

According to Dr. Park, the best predictor of long-term response is disease burden. In ALL, patients with less than 5% leukemia cells in their bone marrow were associated with the best outcomes.

"Almost all high disease–burden patients eventually relapse and then, unfortunately, succumb to the disease," said Dr. Park. "It's really the patients with low disease burden who are enjoying long-term benefit."

Often associated with low disease burden, stable disease at the time of CAR T-cell infusion is another predictor of response.

"Stable disease at the time of infusion is really the key to get the best benefit," said Dr. Park. "While these patients could have high-burden disease, lower burden is obviously better."

Another thing to keep in mind, said Dr. Park, is that pediatric ALL patients tend to do much better than adult patients, even the less refractory patients. The disease is very different in the pediatric population and responds better to therapy, driving a difference in survival. In 2017, tisagenlecleucel (Kymriah), the first ever CAR T-cell product, was approved by the FDA for the treatment of patients under 25 years (Maude et al., 2018).

"We still do not have an approved CAR-T product for adult patients older than 25," said Dr. Park, who emphasized that regardless of the CAR used,

the centers involved, or the manufacturing process, CAR T-cell therapy in ALL has consistently demonstrated an 80% complete response rate and 40% rate of relapse in this population.

DIFFUSE LARGE B-CELL LYMPHOMA

The FDA has also approved two CD19 CAR T-cell products for the treatment of adult patients with relapsed or refractory large B-cell lymphoma, including diffuse large B-cell lymphoma not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and diffuse large B-cell lymphoma arising from follicular lymphoma.

Axicabtagene ciloleucel (Yescarta) was approved in October 2017 based on data from the ZUMA-1 trial that showed an overall response rate of 82% (54% complete response plus 28% partial response) in patients who had received more than two lines of systemic therapy, and tisagenlecleucel (also approved for ALL) was approved in May 2018 for similar indications. Both products target CD19 with the CD28 costimulatory domain.

As Dr. Park explained, with diffuse large B-cell lymphoma, complete responders do much better than patients with a partial response, but the relapse rate (30%) is lower than that seen with ALL (Neelapu et al., 2017).

"We're using the same number of CAR T cells but getting a different response rate," Dr. Park observed. "Although the complete response is only around 50% vs. 80% in ALL, the responses are very durable. These are very exciting data."

PHARMACOTHERAPY IN CYTOKINE RELEASE SYNDROME

CAR T cells have shown the potential to achieve durable responses in heavily pretreated patients, but clinicians should be mindful of serious treatment-related toxicities. As Dr. King reported, cytokine release syndrome is the most prevalent adverse effect following CAR T-cell therapy and must be identified promptly by monitoring patient symptoms, such as fever, rigors, or hypotension, and also lab changes and inflammatory markers, such as C-reactive protein or ferritin or other sophisticated inflammation markers.

"Following diagnosis, there is a delicate balance between mitigating this immune cascade while salvaging the efficacy of CAR T cells," said Dr. King, who noted that early recognition and optimization of supportive care should be consistent among all grades of cytokine release syndrome for patients. "It is important to employ strategies to maximize patient comfort and symptom relief."

The only FDA-approved agent for cytokine release syndrome is tocilizumab (Actemra) and is strongly recommended for patients with grade 2 cytokine release syndrome or beyond, which is cytokine release syndrome that has progressed beyond vasopressors, fluid boluses, and other supportive care management.

Another available agent is siltuximab (Sylvant). An antagonist of interleukin 6, siltuximab is available as an intravenous solution only, said Dr. King, but it is extremely important to note that use is restricted to expert opinion as salvage therapy for cytokine release syndrome that has progressed beyond tocilizumab, glucocorticoids, and supportive care measures.

Finally, the most controversial agent in the management of cytokine release syndrome is glucocorticoids, said Dr. King, who noted that there are two major agents recommended in guidelines: dexamethasone and methylprednisolone. With respect to adverse effects associated with glucocorticoids, Dr. King emphasized that endocrine metabolic effects such as hyperglycemia should be well controlled, especially if a patient is in the intensive care unit. In addition, there is a risk for gastrointestinal hemorrhage and stress ulcers, so patients should be on adequate prophylaxis. Finally, said Dr. King, there is an increased risk for opportunistic infections, especially in this hematologic malignancy patient population. Patients should be on adequate fungal and pneumocystis pneumonia prophylaxis when they are receiving therapy with glucocorticoids.

Because steroids can diminish the expansion of T cells in a healthy patient, there is a concern that using glucocorticoids will limit the effectiveness of CAR T cells. As Dr. King reported, however, some data suggest that corticosteroids might not actually mitigate response to CAR T cells (Neelapu et al., 2018). Nevertheless, she said, it is important to note that more prospective and controlled trials are needed to elucidate this true effect of glucocorticoids on CAR T cells.

"Given the concern for decreased T-cell expansion and decreased efficacy, we use caution with routine glucocorticoid use in this patient population," Dr. King concluded. "Our practice and the expert opinion practice is to reserve steroids only for cytokine release syndrome that is refractory to supportive care and tocilizumab."

Disclosure

Dr. Park has no conflicts of interest to disclose. Dr. King has served on advisory boards for Genentech.

References

Maude, S. L., Laetsch, T. W., Buechner, J., Rives, S., Boyer, M., Bittencourt, H.,...Grupp, S. A. (2018). Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *New England Journal of Medicine, 378*(5), 439–448. https://doi.org/10.1056/NEJMoa1709866

Neelapu, S. S., Locke, F. L., Bartlett, N. L., Lekakis, L. J., Miklos, D. B., Jacobson, C. A.,...Go, W. Y. (2017). Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *New England Journal of Medicine, 377*(26), 2531–2544. https://doi.org/10.1056/NEJMoa1707447

Neelapu, S. S., Tummala, S., Kebriaei, P., Wierda, W., Gutierrez, C., Locke, F. L.,...Shpall, E. J. (2018). Chimeric antigen receptor T-cell therapy – assessment and management of toxicities. *Nature Reviews Clinical Oncology, 15*(1), 47–62. https://doi.org/10.1038/nrclinonc.2017.148

Park, J. H., Rivière, I., Gonen, M., Wang, X., Sénéchal, B., Curran, K. J.,...Sadelain, M. (2018). Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. *New England Journal of Medicine, 378*(5), 449–459. https://www.nejm.org/doi/10.1056/NEJMoa1709919