ADVANCES IN LLM

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

Section Editor: Susan O'Brien, MD

Chimeric Antigen Receptor T-Cell Therapy for T-Cell Acute Lymphocytic Leukemia

Ibrahim Aldoss, MD
Associate Professor
Division of Leukemia
Department of Hematology & Hematopoietic Cell Transplantation
City of Hope
Duarte, California

H&O What are the limitations of current treatments for T-cell acute lymphocytic leukemia (ALL)?

IA Although with modern ALL regimens the outcomes for patients with newly diagnosed T-cell ALL or lymphoblastic lymphoma (LL) are comparable with the outcomes for those with newly diagnosed B-cell ALL, the treatment of patients with relapsed or refractory (R/R) T-cell ALL is still very challenging. Unlike the available salvage options for R/R B-cell ALL, those for R/R T-cell ALL are limited, and outcomes are dismal. Currently, we do not have any approved antibody or cellular therapy for use in this setting. The only drug approved for R/R T-cell ALL is nelarabine, which has a complete response rate of less than 25% when used as a single agent in this setting. Furthermore, we are now including nelarabine as part of frontline therapy in T-cell ALL, making options extremely limited for patients who have R/R disease after initial therapies. Therefore, R/R T-cell ALL represents an area of highly unmet therapeutic need.

H&O What makes chimeric antigen receptor (CAR) T-cell therapy worth pursuing in T-cell ALL?

IA CAR T-cell therapy has emerged as the most effective salvage treatment for patients with advanced B-cell ALL and several other hematologic malignancies, including myeloma and lymphomas. CAR T-cell therapy has been shown to produce high rates of remission in patients with advanced B-cell ALL, and some of these remissions are durable even without allogeneic hematopoietic stem cell transplant consolidation. Therefore, significant interest is being shown in pursuing CAR T-cell therapy for T-cell ALL. This is an especially appealing option for T-cell ALL because these patients are at high risk of having extramedullary disease, and CAR T-cell therapy has shown to be one of the most effective therapeutic approaches in ALL with involvement of extramedullary sites, in which other therapies are usually less active.

H&O Why has the development of CAR T-cell therapy for T-cell ALL lagged that for B-cell ALL?

IA Several limitations exist that are related to the nature of T-cell ALL or LL. Most importantly, T lymphoblasts have surface antigens that are similar to those of the normal T cells that we collect to produce CAR T cells. This similarity can lead to contamination of the autologous product if we accidentally collect malignant cells along with normal T cells. To avoid this risk, some studies have pursued the use of T cells from a healthy donor for the manufacture of CAR T cells, but this approach can place the patient at risk for the development of graft-versus-host disease. The similarity between the surface antigens also raises the concern that the CAR T cells might kill other CAR T cells, a phenomenon we refer to as "fratricide" or "friendly fire."

H&O What are some potential targets for CAR T-cell therapy in T-cell ALL?

IA CD7 is the target that has been used most often for CAR T-cell therapy in T-cell ALL. In addition, researchers are looking at the use of CD5 and CD2 as targets.

H&O What research is looking at the use of CAR T-cell therapy in T-cell ALL?

IA Over the last several years, innovative research has led to the development of novel CAR T-cell products to target R/R T-cell ALL. One example is WU-CART-007, also known as W-T7, from Wugen. This is an off-the-shelf, allogeneic, CD7-targeted CAR T-cells product with CRISPR-Cas9 deletion of both CD7 and the T-cell receptor alpha constant (TRAC). By deleting both CD7 and TRAC, we can prevent fratricide and mitigate the risk of graft-versus-host disease. A global phase 1/2 study examined the use of W-T7 as a treatment for children and adults with R/R T-cell ALL or LL. A total of 13 heavily pretreated patients were treated at the recommended phase 2 dose and received a single infusion of 900 million CAR T cells after enhanced lymphodepletion with cyclophosphamide and fludarabine. In results that were recently presented at the 2024 European Hematology Association Congress, the overall response rate was 91% and the composite complete response (CR) rate was 82%.[1] While in remission, 7 patients were successfully transitioned to transplant, and the median duration of response exceeded 6 months. All patients experienced cytokine release syndrome (CRS), which was grade 1 or 2 in 9 patients (69%) and grade 3 or higher in 4 patients (31%). CRS was successfully managed with corticosteroids, tocilizumab, or anakinra (Kineret, Sobi).

In another study, from Singapore, researchers investigated the use of CAR T-cell therapy that expressed an anti-CD7 CAR and an anti-CD7 protein expression blocker (PEBL) to prevent the fratricide of CAR T cells. In a recently published manuscript in *Nature Medicine*, the authors reported that 16 of 17 patients with R/R T-cell ALL achieved a measurable residual disease (MRD)–negative CR.[2] CD7-negative disease progression developed in the one patient who did not respond. Toxicities were mild, with grade 1 CRS developing in 10 patients and grade 2 CRS in 3 patients. A total of 9 patients received consolidation treatment with an allogeneic stem cell transplant. Remissions were durable, with 11 patients remaining relapse-free at a median follow-up of 15 months.

In a phase 1 study from China, researchers used donor-derived CD7 CAR T cells that were manufactured either from previous stem cell transplant donors or from a new donor.[3] The researchers found that 19 of 20 patients with R/R T-cell ALL achieved a CR, and 7 were able to proceed with transplant. Again, the main toxicity was low-grade CRS.

In a phase 1 study from the United Kingdom, researchers used base editing to create a universal, off-the-shelf CAR T-cell product with specificity for CD7.[4] The researchers were also able to inactivate CD52 receptors, CD7 receptors, and the β-chain of the αβ T-cell receptor. Interim results on the use of this product in 3 children with relapsed leukemia support further investigation of base-edited T-cell therapy for these patients.

H&O What should the next step be in research?

IA We need to conduct registration studies for potential US Food and Drug Administration (FDA) approval so that patients can have access to this effective therapy. We need to evaluate the activity of CAR T-cell therapy in patients with T-cell ALL who have persistent MRD in addition to fully relapsed disease. There is always value in trying novel treatments in the low-disease setting; they are generally more effective and produce more durable remissions and less toxicity. I would also like to see CAR T-cell therapies developed that are aimed at targets beyond CD5 and CD7 because many patients will lose these antigen targets when they experience relapse after CAR T-cell therapy.

Disclosures

Dr Aldoss has received consulting fees from Kite Pharma, Jazz Pharmaceuticals, Syndax Pharmaceuticals, Wugen, AbbVie, Takeda, Amgen, Pfizer, and Adaptive Biotechnologies; and has received research support from MacroGenics, AbbVie, and Jazz Pharmaceuticals.

References

1. Aldoss I, Ghobadi A, Maude S, et al. WU-CART-007, an allogeneic CAR-T cell targeting CD7, is highly effective against relapsed/refractory (R/R) T-cell acute lymphoblastic leukemia/lymphoma (T-ALL/LBL) [EHA abstract S110]. *HemaSphere*. 2014;8(suppl 1).

2. Oh BLZ, Shimasaki N, Coustan-Smith E, et al. Fratricide-resistant CD7-CAR T cells in T-ALL [published online September 3, 2024]. *Nat Med*. doi:10.1038/s41591-024-03228-8.

3. Pan J, Tan Y, Wang G, et al. Donor-derived CD7 chimeric antigen receptor T cells for T-cell acute lymphoblastic leukemia: first-in-human, phase I trial. *J Clin Oncol*. 2021;39(30):3340-3351.

4. Chiesa R, Georgiadis C, Syed F, et al. Base-edited CAR7 T cells for relapsed T-cell acute lymphoblastic leukemia. *N Engl J Med*. 2023;389(10):899-910.