What are the current treatment approaches for patients with refractory aggressive DLBCL?

The standard frontline therapy for diffuse large B-cell lymphoma (DLBCL) is chemoimmunotherapy with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Patients who relapse after R-CHOP receive salvage chemotherapy, followed by an autologous stem cell transplant. Patients with refractory disease are those who never responded to frontline or salvage therapy or relapsed after autologous transplant. Currently, there is no accepted standard of care for these patients. They are usually treated with third-line or fourth-line chemotherapies consisting of agents that were not used in the first- or second-line settings. This approach was associated with an overall response rate of 26%, a complete response rate of 8%, and a median overall survival of 6.6 months in the SCHOLAR-1 study (Retrospective Non-Hodgkin Lymphoma Research), a meta-analysis of 635 patients. These patients therefore have an extremely poor prognosis. There has not been a treatment approved by the US Food and Drug Administration (FDA) for the refractory DLBCL patient population in more than 30 years. There is a huge unmet need for these patients.

What are the principles behind CAR T-cell therapy?

Chimeric antigen receptor (CAR) T-cell therapy is a form of adoptive T-cell therapy in which T cells are genetically engineered to express a CAR. CARs consist of extracellular and intracellular domains. The extracellular domain usually consists of an antibody that targets a protein or an antigen expressed on the surface of the tumor. In B-cell lymphomas, the most common target for CAR T cells is CD19. Other targets under exploration include CD20 and CD22. The intracellular portion of the CAR has 2 domains. The CD3-zeta domain provides signal 1, and the costimulatory domain provides signal 2 for activation of the T cells. CD28 or 4-1BB (CD137) are the most commonly used costimulatory domains for CAR T cells.

The process of preparing CAR T cells begins with obtaining a blood sample from the patient. The CAR molecule is introduced into the patient’s T cells through viral or nonviral approaches. The cells undergo a brief round of expansion in the laboratory and are then infused back into the patient. The T cells become activated when they recognize the target antigen on the surface of the tumor, in this case, CD19. When T cells are activated, they undergo massive expansion in the body. Each CAR T cell can multiply more than a thousand times. In parallel with this proliferation, the cells start to produce multiple different cytokines. These cytokines improve the T cells’ function and also help them traffic to the tumor site. The CAR T cells also start killing the tumor cells by expressing cytotoxic molecules, such as granzymes and perforins.

In what areas has CAR T-cell therapy shown promising results?

Most of the data are currently available in non-Hodgkin lymphomas and leukemias. CAR T-cell ther-
apy has shown strong promise in B-cell non-Hodgkin lymphoma, as well as in B-cell leukemias, including acute lymphoblastic leukemia and chronic lymphocytic leukemia. It has shown efficacy in both aggressive and indolent lymphomas.

**H&O** What is KTE-C19?

The CAR T-cell product KTE-C19, also known as axicabtagene ciloleucel (Kite Pharma), is currently under evaluation in clinical trials. This product was initially developed at the National Cancer Institute (NCI). The extracellular domain consists of a single-chain antibody called FMC-63 that recognizes CD19 on the surface of the tumor cell. The CD3-zeta provides signal 1 for the activation of the T cells, and the CD28 costimulatory domain provides signal 2.

**H&O** What is the design of the ZUMA-1 trial?

The phase 1/2 ZUMA-1 study is the first multicenter trial of CAR T-cell therapy in patients with lymphoma. It evaluated KTE-C19 in patients with refractory, aggressive B-cell non-Hodgkin lymphoma. Eligible patients either did not respond to their previous course of chemotherapy or had relapsed within 12 months of an autologous stem cell transplant. In the phase 1 portion, the primary endpoint was to establish the safety and the maximum tolerated dose of KTE-C19. The aim of the phase 2 trial was to establish efficacy, and the primary endpoint was best overall response rate. Phase 2 study was conducted at 22 sites. There were 2 cohorts. Cohort 1 included patients with refractory DLBCL, and cohort 2 included patients with refractory primary mediastinal B-cell lymphoma and transformed follicular lymphoma, which are also aggressive B-cell non-Hodgkin lymphomas.

**H&O** What have previous analyses of ZUMA-1 shown?

The phase 1 trial enrolled 7 patients with refractory DLBCL from 4 centers. It established the safety of KTE-C19 and demonstrated preliminary efficacy. Results were recently published in *Molecular Therapy*. The complete response rate was 57%, and 43% of patients remained in complete remission at 1 year. Durable responses were also found in a 2015 study conducted by Kochenderfer and colleagues at the NCI. KTE-C19 was tested in a single-arm, single-institution, phase 1/2 trial in patients with aggressive B-cell non-Hodgkin lymphoma. Complete remissions were observed in approximately 45% of patients, with the longest response ongoing at 4 years.

**H&O** What were the results of the interim analysis of the phase 2 data from ZUMA-1?

The results from the interim analysis of the ZUMA-1 phase 2 trial as a late-breaking abstract at the 2016 American Society of Hematology (ASH) meeting. The ZUMA-1 study was designed with a prespecified interim efficacy analysis to be conducted when at least 50 patients in cohort 1—those with DLBCL—had at least 3 months of follow-up. The analysis met its primary endpoint for overall response rate, with a P value of less than .0001 compared with a historical overall response rate assumption of 20%. Subgroup analyses showed complete responses in 75% of patients who relapsed within 12 months after autologous stem cell transplant, and in 47% of patients refractory to second-line or later chemotherapy. Assessment at 3 months showed a complete response rate of 39%; some of the patients who responded initially subsequently relapsed or progressed.

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apheresis to delivery of the manufactured product to the clinical site was 17 days, which is short compared with many of the other CAR T-cell products currently under evaluation.

H&O What were the adverse events in ZUMA-1?

SN There were 2 common adverse events, both of which are seen with any type of CAR T-cell therapy. One was cytokine release syndrome, and the other was neurologic events. In the ZUMA-1 trial, the majority of these adverse events were grade 1 or grade 2. Grade 3 or higher cytokine release syndrome was observed in 13% of patients, and grade 3 or higher neurologic events were observed in 29% of patients. Most of the neurologic events were reversible. Three patients had ongoing grade 1 memory impairment or grade 1/2 tremors.

Excluding those patients who died from lymphoma, 3 patients died after treatment with KTE-C19. Two of the deaths were related to KTE-C19. One patient died of hemophagocytic lymphohistiocytosis, and one died of a cardiac arrest while experiencing cytokine release syndrome. The third patient died from a pulmonary embolism considered unrelated to KTE-C19. The treatment-emergent mortality was 3% in ZUMA-1.

H&O What did the biomarker analysis find?

SN To date, the biomarker analysis performed has shown that the infusion of KTE-C19 was followed by a robust expansion of CAR T cells in the blood. The peak CAR T-cell expansion occurred between 7 to 14 days after infusion. In the patients with an ongoing complete remission at 3 months, the peak number of CAR T cells was 6-fold higher compared with patients who did not have an ongoing complete remission at 3 months. In addition, peak CAR T-cell levels were associated with grade 3 or higher neurologic toxicity, but not with cytokine release syndrome.

We also measured 44 analytes in the serum. Within the first 1 to 2 weeks after KTE-C19 infusion, levels of a number of different cytokines, chemokines, and other immune effector molecules increased in the serum. Most of these cytokine levels returned to baseline by approximately 4 weeks. Increased levels of interleukin (IL) 6 and IL-15 were associated with grade 3 or higher cytokine release syndrome and neurologic toxicity. Additional biomarker analyses are ongoing.

H&O Are the outcomes in ZUMA-1 similar to those seen with other CAR T-cell therapies in lymphoma?

SN The rates of overall response and complete remission in ZUMA-1 were comparable with those seen with CTL019 (Novartis), an agent initially developed at the University of Pennsylvania. Response rates were also comparable with early data for JCAR017 (Juno Therapeutics).

H&O Do you have any recommendations for the clinical use of KTE-C19 and/or CAR T-cell therapy in general?

SN KTE-C19 appears to be highly effective in patients with aggressive B-cell non-Hodgkin lymphoma who are refractory to existing therapies. In fact, the complete remission rate is at least 6-fold higher than that observed in the SCHOLAR-1 study with existing therapies. A significant proportion of responses seem to be durable, based on data from the phase 1 portion of the ZUMA-1 trial, as well as the earlier phase 1/2 study conducted at the NCI.

KTE-C19 is not yet approved by the FDA, so currently it can be administered only in the context of clinical trials. The preparation and education of all the providers involved in the management of these patients is essential before CAR T-cell therapy can be administered at any new center. Like all CAR T-cell therapies, KTE-C19 is associated with cytokine release syndrome and neurologic toxicity, which are not typically seen with traditional chemotherapies, targeted therapies, or monoclonal antibodies. Before KTE-C19 can be administered, it is critical for the physicians and nursing staff to undergo training to recognize, grade, and manage these toxicities. We now know that a central mediator for the cytokine release
syndrome is IL-6. Therefore, the preferred treatment for cytokine release syndrome is anti–IL-6 therapy with either tocilizumab (Actemra, Genentech), an anti–IL-6 receptor antibody, or siltuximab (Sylvant, Janssen), an anti–IL-6 antibody. If anti–IL-6 therapy is not effective for the management of cytokine release syndrome and neurologic toxicity, corticosteroids can be used, although sparingly, as they may decrease the antitumor effects of CAR T-cell therapy.

**H&O** What are the other ZUMA trials evaluating?

**SN** ZUMA-1 primarily enrolled patients with refractory aggressive B-cell non-Hodgkin lymphoma. ZUMA-2 is evaluating KTE-C19 in patients with refractory mantle cell lymphoma. ZUMA-3 and ZUMA-4 are being conducted in patients with acute lymphoblastic leukemia. In the ZUMA-6 study, KTE-C19 is being combined with atezolizumab (Tecentriq, Genentech), a monoclonal antibody of the immunoglobulin G1 isotype against the protein programmed cell death–ligand 1, in patients with DLBCL.

**H&O** Are there any other areas of research evaluating KTE-C19?

**SN** Active areas of investigation include the causes of resistance to KTE-C19 and relapse/progression after initial response. A key question is whether CD19 loss contributes to relapse or progression. Clinical trials are evaluating whether progression or loss of efficacy occurs when T cells become exhausted after interacting with the tumor, and, if so, whether immune checkpoint blockade can reactivate the T cells. It will also be necessary to identify any other intrinsic tumor mechanisms that might cause immune resistance to this product.

There are many areas we would like to understand better to further improve the safety of this product. An active area of investigation is to better understand the pathophysiology of the neurotoxicity that occurs with CAR T-cell therapy. Although neurotoxicity is generally reversible and can be managed conservatively with supportive care, an understanding of the central mediator for this event could allow us to develop better prophylactic and therapeutic approaches. Many investigators are performing extensive analyses of blood samples and cerebrospinal fluid samples to further understand the neurotoxicity associated with CAR T-cell therapy.

**Disclosure**

Dr Neelapu has received research funding and honoraria from and served as a consultant and Scientific Board Member for Kite Pharma.

**Suggested Readings**


