ADVANCES IN LLM

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

Section Editor: Susan O'Brien, MD

Tips on Choosing a CAR T-Cell Therapy in DLBCL

Jeremy S. Abramson, MD
Associate Professor of Medicine
Harvard Medical School
Director of the Lymphoma Program
Massachusetts General Hospital Cancer Center
Boston, Massachusetts

H&O What chimeric antigen receptor (CAR) T-cell therapies are approved for diffuse large B-cell lymphoma (DLBCL), and how do they differ?

JA There are 3 approved CAR T-cell therapies for patients with DLBCL in the third-line or later setting. These are primarily chemotherapy-refractory patients who previously had no viable curative options available. In that space, axicabtagene ciloleucel (axi-cel; Yescarta, Kite), lisocabtagene maraleucel (liso-cel; Breyanzi, Juno/BMS), and tisagenlecleucel (tisa-cel; Kymriah, Novartis) all earned initial US Food and Drug Administration (FDA) approvals based on the high rates of complete response (CR) and durable remission in the ZUMA-7, TRANSFORM, and BELINDA trials, respectively. Collectively, these 3 trials demonstrated that patients once considered incurable could indeed be cured with CAR T-cell therapy despite having multiply relapsed/refractory DLBCL. Patients had a median of 3 prior lines of therapy, so most of them were being treated in the fourth line or later. The efficacy observed here naturally raises the prospect of administering CAR T-cell treatment earlier in the course of therapy, before patients have experienced the negative effects of sequential lines of chemotherapy.

Three pivotal randomized phase 3 trials were subsequently conducted to evaluate CAR T-cell therapy as a second-line treatment, specifically in high-risk patients with primary refractory DLBCL or those who relapsed within 1 year and were considered eligible for autologous stem cell transplant (ASCT). The standard of care (SOC) comparator in these trials was platinum-based chemotherapy followed by high-dose chemotherapy and ASCT for chemosensitive disease—the longstanding SOC in second-line DLBCL. Modern studies, however, have shown a very low likelihood of successful outcomes with this SOC approach. All 3 trials randomized patients to either SOC, or 1 of the 3 CAR T-cell therapies.

The BELINDA trial (tisa-cel) yielded entirely negative results, but, both ZUMA-7 (axi-cel) and TRANSFORM (liso-cel) showed a dramatic improvement in event-free survival (EFS), progression-free survival (PFS), and the CR rate compared with SOC, leading to FDA approval of both axi-cel and liso-cel as second-line treatments for patients with primary refractory or early relapsed large B-cell lymphoma (LBCL) within 1 year of initial treatment. After extended follow-up, the ZUMA-7 trial demonstrated an overall survival (OS) benefit favoring axi-cel over SOC. A difference between ZUMA-7 and TRANSFORM is that ZUMA-7 did not allow crossover, whereas TRANSFORM had built-in crossover, which allowed patients to immediately crossover to receive liso-cel if the SOC failed. As a result, all patients underwent apheresis before randomization and could immediately transition. This scenario introduces potential complexity into the OS analysis, given that most patients assigned to the SOC experienced treatment failure and crossed over to receive liso-cel at a median of only 14 days. However, after adjusting for the impact of crossover, the

TRANSFORM trial also showed evidence of OS favoring liso-cel.

I find these data to be highly compelling, suggesting that either axi-cel or liso-cel should now be the preferred second-line treatment for patients with primary refractory or early relapsed LBCL. That includes DLBCL, high-grade B-cell lymphomas with double- or triple-hit genetics, and primary mediastinal B-cell lymphomas. Although tisa-cel should not be used in the second-line setting, all 3 products remain approved and available in the third-line setting for patients who have not previously undergone CAR T-cell therapy as a second-line treatment.

> In the second and third line or later, CAR T-cell therapy has truly revolutionized the field compared with the standard of care options that were previously available.

H&O How does the efficacy of CAR T-cell therapy compare with other standard treatments?

JA When these treatments are applied in the second-, third-, or later-line setting for LBCL, CAR T-cell therapies are far superior to the conventional therapies that were previously available. In the third line or later, data from the retrospective SCHOLAR-1 study suggest that conventional therapies in a similar chemotherapy-refractory patient population induce CR rates of less than 10%, with an OS of 6 months or less. This is a stark contrast to the outcomes associated with CAR T-cell therapy, where both axi-cel and liso-cel produce CR rates of more than 50% and OS that is far prolonged compared with historical therapies. In the second-line or later setting, we have randomized data that show superior PFS, EFS, CR rate, and OS of axi-cel and liso-cel compared with the SOC for patients with primary refractory disease or disease relapsing within 12 months of initial treatment. Of note, the phase 2 PILOT study specifically evaluated liso-cel as second-line therapy in transplant-ineligible patients who would have been excluded from the ZUMA-7 and TRANSFORM trials. These patients were older, had medical comorbidities, and did not have a curative option in the second-line setting. Notably, this study showed an encouraging CR rate of more than 50%, and a durable PFS that was far superior to that seen with conventional therapies. These data suggest that in the second and third line or later, CAR T-cell therapy has truly revolutionized the field compared with the SOC options that were previously available.

H&O What are some pros and cons of CAR T-cell therapy for treating patients with DLBCL?

JA Two advantages to using CAR T-cell therapy are that it works better than everything else in this particular context, and that it is a one-time treatment. A notable disadvantage lies in that it can be a complicated treatment to administer. It involves a multistep process: apheresis of a patient's blood, sending the blood to a centralized manufacturing facility operated by a commercial product maker, and subsequently reintroducing those modified cells back into the patient following lymphodepleting chemotherapy. This process can take anywhere from 3 to 6 weeks, depending on the product. This time frame can pose a challenge for patients with aggressive lymphomas that are likely to continue to progress, and for those who are chemotherapy-refractory, because maintaining disease control until the CAR T-cell product becomes available can prove quite taxing. In such cases, we use bridging therapy, which involves administering a minimally toxic treatment to control the disease and allow sufficient time for the CAR T-cell product to be prepared and administered back to the patient. However, many patients might not respond sufficiently to it. Their disease could progress, and unfortunately, they may even die while awaiting CAR T-cell treatment because of the time required.

Another drawback is related to toxicity. The primary toxicities associated with CAR T-cell therapies are cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Both conditions are related to the release of inflammatory cytokines that can induce fever and other clinical challenges. If not addressed, they may progress to induce low blood pressure, organ dysfunction, and altered mental status. These side effects are generally reversible using the interleukin 6 (IL-6) antibody tocilizumab (Actemra, Genentech) and corticosteroids. Over time, we have learned to intervene earlier than we did in the initial pivotal trials. We now know that treating CRS earlier does not impair the efficacy of the CAR T-cell treatment. Neurologic toxicities manifest somewhat later than CRS. These may result in confusion and difficulty with word-finding, and in severe states can progress to seizures or coma. This can be concerning and frightening, but it is also reversible. The primary treatment for this is corticosteroids plus medications to prevent seizures.

It is worth noting that there are differences across the various CAR T-cell products. Axi-cel uses a CD28 costimulatory domain and is associated with higher rates and severity of CRS and neurotoxicity when compared with liso-cel and tisa-cel. Both liso-cel and tisa-cel use a 4-1BB costimulatory domain, which leads to a more gradual expansion of the CAR T-cell products and a milder toxicity profile. Liso-cel is likely to have lower rates of toxicity, which is important for patients who are notably older, are frail, and might not tolerate the toxicity of axi-cel well.

A patient's fitness, organ function, and baseline bone marrow function need to be assessed; however, this is true for any treatment in oncology or medicine: patients must be healthy enough to tolerate treatment. Among other side effects, prolonged low blood counts are quite common, affecting approximately 30% to 40% of patients. This likely stems from the use of fludarabine and cyclophosphamide as lymphodepleting chemotherapy before the CAR T-cell infusion, as well as the effect of CAR T-cell–associated inflammation on the bone marrow.

Another con is cost. Although it may be difficult to consider this on a patient-by-patient basis, it is important to acknowledge the substantial expenses associated with these therapies. The healthcare system must absorb these costs to make these truly transformational and often life-saving treatments accessible to patients.

H&O Are any of the studies you mentioned ongoing, and what other studies are looking into CAR T-cell therapy for patients with DLBCL?

JA Ongoing follow-up is being conducted across all these studies to evaluate their long-term effects. In the third-line or later setting, the ZUMA-1 trial now has 5-year follow-up data showing durable remissions and disease-specific survival of greater than 50%. These data are compelling and highlight that with ongoing follow-up, these products offer the opportunity for a cure. The second-line ZUMA-7 and TRANSFORM studies established liso-cel and axi-cel as the new preferred SOC treatments for patients with primary refractory or early relapsed LBCL eligible for CAR T-cell therapy. However, further extended follow-up is needed to assess the well-being of these patients down the line and to understand the potential long-term cure rate. In the context of nontransplant-eligible patients, where only the PILOT trial data are available, additional data are crucial. It also would be nice to see how CAR T-cell therapy compares with bispecific antibody treatments in that population.

At present, ongoing studies are not those pivotal trials. An earlier, upfront study called the ZUMA-23 trial is in progress, comparing axi-cel with SOC chemoimmunotherapy in high-risk patients with previously untreated DLBCL. This study will determine whether CAR T-cell therapy should be incorporated into frontline therapy in selected high-risk patients. We look forward to these data, but their release is not right around the corner.

Numerous other studies are looking at CAR T-cell therapy in combination with available pharmacologic agents, such as immune checkpoint inhibitors, immunomodulators, and tyrosine kinase inhibitors. Additionally, several ongoing trials are looking at newer CAR T-cell constructs that might overcome some of the liabilities of earlier CAR T-cell therapies, including off-the-shelf CAR T-cell products that do not require a manufacturing period owing to using healthy donor cells as opposed to autologous cells.

H&O What type of DLBCL patients are suitable candidates for CAR T-cell treatment? Are there any factors that could make a patient ineligible?

JA In the second-line setting, the first question we used to ask was whether a patient was eligible for a transplant or not. If the patient was eligible, we would do platinum-based chemotherapy followed by high-dose chemotherapy, and stem cell transplant if the patient had chemotherapy-sensitive disease. If the patient was not eligible, we would do palliative-intent chemotherapy. That paradigm has shifted based on the TRANSFORM and ZUMA-7 trials. Now, if I have a patient who is relapsing after frontline therapy, my first question is whether the patient has primary refractory disease or has relapsed within 1 year. If the patient has, the next question is whether the patient is eligible for a CAR T-cell therapy based on the TRANSFORM and ZUMA-7 trials. Most patients who are transplant-ineligible are eligible for a CAR T-cell product, and we would use liso-cel or axi-cel. The trials have primarily included patients with a performance status (PS) of 0 to 1. Most of us are comfortable taking patients with a PS of 0 to 2. If patients have a worse PS, then they are probably not great candidates for CAR T-cell therapy or most other intensive treatments. Patients also need to have sufficient bone marrow and organ function. They can certainly have cytopenias and modest impairment of renal, hepatic, or cardiac function, but they need to be able to tolerate the toxicities of treatment and the lymphodepleting chemotherapy.

H&O What key elements should be considered when choosing a CAR T-cell product for patients with DLBCL?

JA The most effective products on prospective and retrospective analyses are axi-cel and liso-cel. Tisa-cel does not have the same rate of CR or PFS in DLBCL. I typically

no longer use tisa-cel in the context of LBCL; instead, I lean toward axi-cel and liso-cel as preferred products. When thinking about selecting a product, the best CAR T-cell product for a patient is honestly the one that is most available to them. If a treating center offers liso-cel but not axi-cel, or vice versa, then obviously the CAR T-cell that is available is the appropriate choice for the patient. Other considerations include toxicity. We see higher rates of both any-grade and severe CRS and neurologic toxicity with axi-cel when compared with liso-cel, even though the efficacy appears quite analogous. In general, I prefer liso-cel because it is a safer product. With that said, there are noteworthy aspects to axi-cel. It is a highly effective product, and its manufacturing process is extremely reliable. Axi-cel has the fastest manufacturing period and turnaround time, along with the lowest rate of unsuccessful manufacturing. If I have a patient who is in significant need of a CAR T-cell product as quickly as possible and cannot afford any delays due to nonconforming product issues, then axi-cel would be my preferred choice. In situations where there is sufficient time available for the patient, I prefer a product with lower rates of toxicity, thus favoring liso-cel.

H&O Are there any genetic mutations that influence which CAR T-cell treatment is a better choice for DLBCL?

JA There are no specific mutations that we look at. All high-risk patients can respond well to CAR T-cell therapy. One significant factor we consider in DLBCL is *TP53* mutations, which are linked to poor outcomes and may adversely affect results with CAR T-cell therapy. We also know that patients with double or triple-hit lymphoma, meaning rearrangements of *MYC* and *BCL2* and/or *BCL6*, typically experience inferior outcomes when treated with conventional therapies. In contrast, CAR T-cell therapy seems to work similarly well in the third-line or later setting. In the second-line setting, those patients may have a higher risk of treatment failure, although CAR T-cell therapy is still markedly better than the prior SOC. Although there are some high-risk genetic and cytogenetic features in DLBCL, none of them either negate the potential efficacy for CAR T-cell therapy or point to a selected benefit for one CAR T-cell treatment over another. As long as patients meet the eligibility for a CAR T-cell product based on their second- or third-line indication, I would favorite CAR T-cell therapy regardless of their genetic or cytogenetic risk factors.

H&O Is CAR T-cell therapy ever used in the first-line setting? How does a patient's disease stage or progression influence the choice of what CAR T-cell product to use?

JA No, CAR T-cell therapy currently does not have a role as initial treatment. It is used only in the relapsed/refractory setting. The ZUMA-23 trial is investigating this important question by specifically looking at patients with high-risk International Prognostic Index (IPI) scores. These patients will be randomized after an initial bridging cycle of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), with the options being continuing either with standard R-CHOP or axi-cel. This trial represents the first randomized study that will likely provide insights into whether CAR T-cell therapy as part of initial treatment is superior to the historical SOC.

Previously, the ZUMA-12 trial was conducted, involving high-risk patients with either high-risk IPI scores or double- or triple-hit lymphoma. In this trial, patients received initial cycles of R-CHOP or dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (EPOCH-R). If patients achieved less than a CR, a phase 2 design led them to CAR T-cell treatment with axi-cel, resulting in excellent outcomes. These were better than what might have been expected with continued chemoimmunotherapy, although it is impossible to ascertain in the absence of a randomized trial. The ZUMA-23 trial has the potential to change the SOC in the frontline setting. However, chemoimmunotherapy remains the preferred upfront approach as of now. This includes options like R-CHOP and polatuzumab vedotin (Polivy, Genentech), rituximab, cyclophosphamide, doxorubicin, and prednisolone (pola-R-CHP) as a newer option for high-IPI patients, and in some cases, dose-adjusted EPOCH-R, particularly for patients with double- or triple-hit lymphomas or primary mediastinal B-cell lymphomas.

H&O Can you discuss the risks or side effects associated with CAR T-cell therapy, and how they are managed?

JA For managing CRS, we use tocilizumab (Actemra, Genentech) in combination with corticosteroids. Corticosteroids alone are the standard approach for managing neurologic toxicities. Other toxicities we consider are prolonged cytopenias. Some patients may require growth factor stimulation and time for their blood counts to recover. In cases of significantly prolonged cytopenias, we consider bone marrow biopsies to rule out any underlying issues. In addition to low blood counts, the risk of infections is a concern. These patients may take a long time to recover their healthy T-lymphocyte counts, leaving them vulnerable to infections. To address this, I keep these patients on protective antibiotics until their CD4 count has sufficiently recovered. I ensure that they receive the

appropriate vaccines and stress the importance of ongoing precaution against infection because the elevated risk for one can persist up to 6 months after treatment or longer. These late toxicities, particularly late infections, are increasingly recognized as issues that can affect patients after achieving efficacy milestones. We must remember that these patients continue to have ongoing immune defects that warrant counseling and ongoing protection.

H&O How does the cost and accessibility of CAR T-cell therapy impact patients and their providers?

JA Cost and accessibility pose significant challenges in the realm of CAR T-cell treatment. These therapies are not available everywhere. If we examine the availability of products like axi-cel or liso-cel, they are not offered at most centers in the United States. Patients who live on the coasts tend to have more readily available options, whereas access in the middle of the country remains sparse. Internationally, some countries have access to CAR T-cell therapy, but the majority still lack access. The primary barrier to broader accessibility is, undoubtedly, cost.

I think a critical step forward is to make CAR T-cell therapy more accessible. It is a shared belief that the majority of patients who would benefit from CAR T-cell therapy in DLBCL in the second- or third-line setting do not properly get referred in the first place because they do not live near a CAR T-cell treating center, and they may not be interested in traveling a long distance to get there because of the associated time, effort, and cost. To bridge this gap, we must bring these products closer to where patients live. I am confident we will do that. Exploring safer ways to administer these products more often in the outpatient setting will help reduce costs and also minimize healthcare utilization. Specifically, products like liso-cel and tisa-cel, with lower rates of toxicity, are more amenable to outpatient therapy. Expanding access by integrating these treatments into regional hospitals, closer to where patients live, will be a significant step forward. You need the right infrastructure and supportive care network to be able to handle and store the cellular product, complete with a blood bank and a transfusion center. A multidisciplinary team is also essential, including care specialists who can help in all levels of patient care, including toxicity management and critical care, as well as social workers, nurses, and trained professionals to help navigate the complexities of the CAR T-cell treatment process. There is a lot of room to move on this. If patients are fortunate enough to live within an hour of a CAR T-cell treating center, they gain access to terrific advances. We need to make these advances more accessible to patients across the United States and worldwide to continue to provide this transformative therapy.

Disclosures

Dr Abramson has consulted for AbbVie, AstraZeneca, BeiGene, Bristol Myers Squibb, Caribou Biosciences, Cellectar Biosciences, Century Therapeutics, Epizyme, Genentech, Genmab, Incyte, Interius BioTherapeutics, Janssen, Kite Pharma, Lilly, and Takeda; and has received research support (to institution) from Bristol Myers Squibb, Cellectis, Merck, Mustang Bio, and Seagen.

Suggested Readings

Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet*. 2020;396(10254):839-852.

Abramson JS, Solomon SR, Arnason J, et al. Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study. *Blood*. 2023;141(14):1675-1684.

Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood*. 2017;130(16):1800-1808.

Bishop MR, Dickinson M, Purtill D, et al. Second-line tisagenlecleucel or standard care in aggressive B-cell lymphoma. *N Engl J Med*. 2022;386(7):629-639.

FDA approves axicabtagene ciloleucel for second-line treatment of large B-cell lymphoma. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-axicabtagene-ciloleucel-second-line-treatment-large-b-cell-lymphoma. Updated April 1, 2022. Accessed August 27, 2023.

FDA approves lisocabtagene maraleucel for relapsed or refractory large B-cell lymphoma. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lisocabtagene-maraleucel-relapsed-or-refractory-large-b-cell-lymphoma. Updated February 5, 2021. Accessed August 27, 2023.

FDA approves tisagenlecleucel for adults with relapsed or refractory large B-cell lymphoma. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tisagenlecleucel-adults-relapsed-or-refractory-large-b-cell-lymphoma. Updated May 3, 2018. Accessed August 27, 2023.

Neelapu SS, Jacobson CA, Ghobadi A, et al. Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma. *Blood*. 2023;141(19):2307-2315.

Neelapu SS, Dickinson M, Munoz J, et al. Axicabtagene ciloleucel as first-line therapy in high-risk large B-cell lymphoma: the phase 2 ZUMA-12 trial. *Nat Med*. 2022;28(4):735-742.

Sehgal A, Hoda D, Riedell PA, et al. Lisocabtagene maraleucel as second-line therapy in adults with relapsed or refractory large B-cell lymphoma who were not intended for haematopoietic stem cell transplantation (PILOT): an open-label, phase 2 study. *Lancet Oncol*. 2022;23(8):1066-1077.

Westin J, Jacobson CA, Chavez JC, et al. ZUMA-23: a global, phase 3, randomized controlled study of axicabtagene ciloleucel versus standard of care as first-line therapy in patients with high-risk large B-cell lymphoma [ASCO abstract TPS7578]. *J Clin Oncol*. 2023;(41)(16)(suppl).

Westin J, Oluwole OO, Kersten MJ, et al. Primary overall survival analysis of the phase 3 randomized ZUMA-7 study of axicabtagene ciloleucel versus standard-of-care therapy in relapsed/refractory large B-cell lymphoma [ASCO abstract LBA107]. *J Clin Oncol*. 2023;(41)(7)(suppl).