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Autologous and Allogeneic CAR T-Cell Therapies: Spotlighting the "Brain-to-Vein" Time

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H&O How has the introduction of chimeric antigen receptor (CAR) T-cell therapy impacted the management of patients with lymphoma?

ML CAR T-cell therapy has revolutionized the opportunity for another chance at cure among patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). The long-term benefits are currently less clear in other lymphomas, such as follicular lymphoma and mantle cell lymphoma. The best opportunity to cure DLBCL is with the first-line therapy. The treatment paradigm may be shifting in the frontline setting, which should hopefully lead to higher cure rates over time. Using history as a guide, the introduction of rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) as first-line treatment negatively impacted second-line outcomes among patients with relapsed or refractory disease. The POLARIX study compared polatuzumab vedotin-piiq (Polivy, Genentech) plus rituximab, cyclophosphamide, doxorubicin, and prednisone (CHP) vs R-CHOP in patients with previously untreated DLBCL. Based on the lack of early separation of the progression-free survival (PFS) curves for polatuzumab plus R-CHP, induction therapy appeared to not change the natural history of primary refractory disease among patients in need of rapid access to therapies other than our standard chemotherapies. Nevertheless, after a median follow-up of 28.2 months, the rate of PFS was 76.7% with polatuzumab plus R-CHP vs 70.2% with R-CHOP at 2 years (stratified hazard ratio [HR] for progression, relapse, or death, 0.73 by Cox regression; 95% CI, 0.57-0.95; *P*=.02). Overall survival at 2 years was not significantly different between the groups.

Two recent phase 3 trials of CAR T-cell therapy challenging second-line chemotherapy, high-dose therapy, and autologous stem cell rescue in early relapsed or refractory DLBCL met their primary endpoints of event-free survival. The ZUMA-7 trial evaluated axicabtagene ciloleucel (Yescarta, Kite) and the TRANSFORM trial evaluated lisocabtagene maraleucel (Breyanzi, Bristol Myers Squibb). In the ZUMA-7 trial, at a median follow-up of 24.9 months, the median event-free survival was 8.3 months with axicabtagene ciloleucel vs 2.0 months with the standard of care. The 24-month event-free survival was 41% vs 16%, respectively (HR for event or death, 0.40; 95% CI, 0.31-0.51; *P*<.001). In the TRANSFORM trial, the median EFS was 10.1 months with lisocabtagene maraleucel vs 2.3 months with the standard of care (HR, 0.349; *P*<.0001).

The BELINDA trial compared tisagenlecleucel (Kymriah, Novartis) vs the standard of care in patients with aggressive B-cell non-Hodgkin lymphoma. The trial did not meet its primary endpoint of event-free survival.

It appears that at least the axicabtagene ciloleucel and lisocabtagene maraleucel CAR T-cell therapies may afford a second chance of cure in this high-risk patient population, who may succumb to their disease within 6 months according to retrospective data. Especially concerning was

the double-refractory population, who likely would struggle to live long enough to receive an approved CAR T-cell therapy or commercial product. It has been monumental to see not only the advances in the efficacy and durability of CAR T cells given in the third-line setting and beyond, but also how the CAR T-cell community has worked together to learn how to mitigate the risks of CAR T-cell toxicities. The rates of grade 3/4 cytokine release syndrome and immune effector cell–associated neurotoxicity syndrome have certainly decreased. Improvements in the side effect profile impact both the patient and the health care system, decreasing the duration of hospitalization after infusion of the CAR T cells and resource utilization. A goal of treatment with improved toxicity management strategies is now to move administration of CAR T-cell therapy from an inpatient setting to an outpatient setting. This goal has been achieved in several CAR T-cell centers across the United States.

In addition to DLBCL, CAR T-cell therapy has also been impactful in other subtypes of lymphoma that allow targeting of CD19. Other autologous products are expanding the targeted antigens beyond CD19 to include CD20 and CD22. Researchers are also trying to enhance the currently available CAR T cells by adding adjunctive therapies to increase the complete response rate, which could raise and then lengthen the median PFS curves. In the phase 1/2 ZUMA-1 trial of axicabtagene ciloleucel in refractory DLBCL, the curve in the third-line setting shows an encouraging plateau with the longest follow-up. The objective response rate was 82%, including a complete response in 54%. At a median follow-up of 15.4 months, a continued response was reported in 42% of patients, including a complete response in 40%. Similar durability has been reported for lisocabtagene maraleucel and tisagenlecleucel but with shorter, yet respectable, follow-up. There is certainly room for improvement in the first 6 months after infusion with any commercially approved CAR T-cell therapy. Therefore, we should not stop trying to develop CAR T cells that target different antigens or have different costimulatory or autocrine loop-type systems.

H&O What are the limitations to the current autologous CAR T-cell products?

ML One limitation concerns the vein-to-vein time, which refers to the duration between apheresis of native T cells, the manufacture of CAR T cells, and then infusion of the CAR T-cell product. Researchers are attempting to shorten the vein-to-vein time for the currently approved agents. However, there are logistical challenges involved with obtaining the T cells from the patient, shipping them to a facility, and processing them for manufacture. There is also a quality-assurance process to ensure that the specimens meet release specifications set for each product by the regulatory bodies.

In clinical trials and commercial environments, I think the vein-to-vein time has been optimized. Clinical practice, however, involves some extra steps. What I call the "brain-to-vein" time begins when the oncologist and the patient agree that CAR T-cell therapy is the preferred next treatment option. The next steps are to gain approval from the patient's insurance company and, for many institutions, to negotiate a single-case agreement with the patient's insurance. These approvals can take weeks. This period is unaccounted for in clinical trials, and it is difficult to assess in real-world analyses. However, I believe that this period strongly impacts the success of treatment. In addition, information is lacking for how the pre-apheresis therapies administered in the brain-to-vein period might impact the health and/or manufacturing fidelity of the CAR T cells. In the end, physicians who administer CAR T cells must balance the need to get the patient to apheresis with the knowledge that the therapies needed to do so might decrease the chances of efficacy in the setting of little to no data. For many physicians, this quandary can lead to sleepless nights.

On the horizon is a formidable challenger, the allogeneic CAR T-cell product. A potential advantage of an allogeneic CAR T-cell product is that the T cells were not damaged by chemotherapy that was administered earlier in the treatment course or to enable the patient to get to apheresis. I fear, though, that the same brain-to-vein time issues will still exist for allogeneic CAR T-cell products.

The brain-to-vein time should supersede the vein-to-vein time as a better indicator of the success of treatment with CAR T-cell therapy. We should be speaking a language of "intent to administer CAR T cells," as the true denominator. We must band together to shorten this time and report it in trials for both the autologous CAR T-cell products and the allogeneic CAR T-cell products that are under investigation.

H&O What are the potential benefits of allogeneic CAR T-cell products?

ML Researchers are currently investigating the first generation of allogeneic or "off-the-shelf" CAR T-cell products. A goal is to produce a product that can prevent graft-vs-host disease (GVHD), while still allowing expansion of the T cells. It is necessary to circumvent the native immune system, so that the foreign T cells are not cleared from the body before they can target the B-cell lymphoma. There are interesting scientific strategies, such as nuclease and CRISPR-based editing technologies. It still amazes me

how quickly these technologies have moved from mouse to man, a credit to the cellular therapy frontline researchers.

Allogeneic CAR T-cell therapies may be readily available for administration. Patients would not need to undergo apheresis and wait for the product to be manufactured. The vein-to-vein time could be eliminated. However, the brain-to-vein time might still be a concern. As an example, the fastest manufacturing time goes to axicabtagene ciloleucel, at approximately 16 or 17 days. It may become paramount to eliminate this delay in a disease that does not care that it is a holiday or a weekend.

H&O What are some of the allogeneic CAR T-cell products under investigation?

ML The phase 1/2 ALPHA-2 study is evaluating ALLO-501A, an anti-CD19 allogeneic CAR T-cell therapy, and ALLO-647, an anti-CD52 monoclonal antibody, among patients with relapsed/refractory DLBCL. This product is made with a proprietary editing technology that removes the native T-cell receptor and CD52, an antigen expressed on the T cells. ALLO-647 attempts to clear the native T cells, similar to the intent of lymphodepletion with cyclophosphamide and fludarabine. The product is then infused into the patients. Preliminary results were presented at the 2021 American Society of Hematology annual meeting. At the time of this interview, 6 participants were in the single-dose cohort and 6 participants were in the consolidation-dose cohort. The overall response rate was 50%, which consisted of complete responses. In the consolidation cohort, the overall response rate was 66.7%, all complete responses. All 3 partial responses converted to a complete response after consolidation. The investigators concluded that ALLO-501A with consolidation dosing demonstrated comparable safety and an improved efficacy profile compared with single dosing.

An adjunctive approach incorporating subsequent dosing to reinvigorate the CARs is an interesting concept that has been previously evaluated with the autologous CAR T-cell products. Based on studies of early allogeneic CAR T-cell dosing, repeated dosing may be needed to chip away at the disease. The process is different in lymphoma vs acute lymphocytic leukemia. In lymphoma, several waves of CAR T cells are likely needed to "peel the onion" of the lymph node. A first wave must be followed by a consistent supply of CAR T cells. The supply can consist of either robust expansion and/or reinvigoration of exhausted cells by adjunctive therapies. Treatment can involve reinfusion with the same allogeneic CAR T-cell product, assuming that the body will not reject these cells as foreign and attempt to eradicate them. Researchers are trying to create CAR T cells that can operate in "stealth mode," meaning they can target the lymphoma cell while evading the immune system that would try to clear them. The CRISPR CTX110 product has removed the native T-cell receptor and beta-2-microglobulin on the cell surface. The novel agent PBCAR0191 was also designed with a genome editing platform. Responses have been reported with this product. Researchers are studying methods to improve the persistence of T cells and evaluating whether multiple dosing strategies are needed.

H&O Are toxicities improved with allogeneic CARs?

ML An important finding in reports of allogeneic CAR T cells is the low rates of GVHD, which is a risk during treatment with any allogeneic product. The science beyond how these products evade the immune system is intriguing. In general, the toxicities of allogeneic CAR T-cell therapies appear to be mostly grade 1/2. There have been low rates of grade 3/4 toxicities. There are on-target effects, as shown by reports of infections. These toxicities can also be seen with autologous products.

H&O What are the challenges in developing allogeneic CAR T-cell therapy?

ML There are several challenges associated with this therapy. In theory, gene editing should help reduce the risk of GVHD and alter the immune system's ability to attack and degrade the CAR T cells. The question is how to transition from clinical trials to commercialization of these products. The major challenge I see is the registrational pathway. In the setting of relapsed or refractory DLBCL, sponsors may choose to perform single-arm phase 2 trials rather than randomized trials that compare these products with an autologous CAR T-cell therapy or another approved treatment that targets CD19, such as loncastuximab tesirine-lpyl or tafasitamab-cxix plus lenalidomide. I would encourage investigators to push for randomized trials, which would ensure that the best therapies move forward. There was minimal homogeneity across the patient populations enrolled in the trials that led to approval by the US Food and Drug Administration in the third-line setting, with similar definitions of endpoints of disease-specific interest. It would be helpful to perform randomized clinical trials in similar patient populations. It is not known whether the regulatory bodies will require these types of trials. In oncology, multiple products have been approved based on data from single-arm phase 2 trials when comparative data or products are lacking. This paradigm I think will shift in relapsed/refractory DLBCL, where several products with activity, including both cellular and noncellular therapies, are now commercially available.

H&O What are the remaining questions regarding the use of allogeneic CAR T-cell therapies?

ML Treatment with allogeneic CAR T-cell therapies has led to responses, but questions remain regarding their durability. The autologous CAR T-cell therapies have set a high bar for durability, but their Achilles' heel remains the unaccounted-for brain-to-vein time. Relapses within the first 6 months are devastating. It might be possible to improve treatment outcomes with a blended approach, in which a first infusion with allogeneic CAR T cells is followed by an infusion of autologous CAR T cells for persistence.

All of the allogeneic CAR T-cell products must find a path to use in the clinic. These projects might do well in clinical trials. However, autologous CD19-directed CAR T-cell therapies are approved in the United States and many other countries. The trials of allogeneic CAR T-cell products limit enrollment to patients who may have already received prior treatment with a CD19-directed CAR T-cell therapy in the relapsed or refractory space, which in my opinion sets them up for failure. It is encouraging to see that some of these studies are now starting to extend enrollment to patients who received prior CD19-directed CAR T-cell therapy or even therapies that act through engagement of CD19. Newly approved agents targeting CD19 include the monoclonal antibody tafasitamab-cxix (Monjuvi, Morphosys/Incyte), which is used in combination with lenalidomide (Revlimid, Celgene), and the CD19 antibody-drug conjugate loncastuximab tesirine-lpyl (Zynlonta, ADC Therapeutics). The question is how patients who develop progressive disease during treatment with a CD19-targeted agent will respond to subsequent treatment with CAR T-cell therapy that also targets CD19. More data will likely be generated from real-world settings, and it is unlikely that this question will be addressed in a clinical trial.

H&O What are some considerations when selecting treatment?

ML When selecting treatment for patients, it is necessary to balance the known efficacy and durability of the approved CAR T-cell therapies vs the potential benefits of allogeneic CAR T-cell therapy. There are commercially approved CAR T-cell therapies that arguably are curable in patients with relapsed/refractory DLBCL. Currently, there are many dose-escalation phase 1 trials of cellular therapy. It can be a difficult choice for clinicians. Researchers should focus on regions that lack access to commercial CAR T-cell therapies to build the initial wave of data to determine the optimal dose and toxicity profile, as well as to glean signals of efficacy.

H&O Do you have any other recommendations regarding the use of CAR T-cell therapy?

ML A hybrid approach using an allogeneic CAR T-cell therapy followed by an autologous CAR T-cell therapy is an interesting idea. However, the brain-to-vein time remains an understudied area. Losing a patient during the brain-to-vein time is incredibly hard emotionally, not only for the patient and their family, but also for the physician/investigator. The data to date do not capture these situations very well, and therefore contemporary reports fail to honor these losses. The failure to highlight the brain-to-vein time discussion within both research and commercial environments is an oversight that the CAR T-cell community must address.

Disclosure

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Suggested Readings

CRISPR therapeutics reports positive results from its phase 1 CARBON trial of CTX110™ in relapsed or refractory CD19+ B-cell malignancies. https://crisprtx.gcs-web.com/news-releases/news-release-details/crispr-therapeutics-reports-positive-results-its-phase-1-carbon. Accessed February 11, 2022.

Jain N, Kantarjian H, Solomon SR, et al. Preliminary safety and efficacy of PBCAR0191, an allogeneic 'off-the-shelf' CD19-directed CAR-T for patients with relapsed/refractory (R/R) CD19+ B-ALL [ASH abstract 650]. *Blood*. 2021;138(suppl 1).

Kamdar M, Solomon SR, Arnason JE, et al. Lisocabtagene maraleucel (liso-cel), a CD19-directed chimeric antigen receptor (CAR) T cell therapy, versus standard of care (SOC) with salvage chemotherapy (CT) followed by autologous stem cell transplantation (ASCT) as second-line (2L) treatment in patients (Pts) with relapsed or refractory (R/R) large B-cell lymphoma (LBCL): results from the randomized phase 3 TRANSFORM study [ASH abstract 91]. *Blood*. 2021;138(suppl 1).

Lekakis LJ, Locke FL, Tees M, et al. ALPHA2 study: ALLO-501A allogeneic CAR T in LBCL, updated results continue to show encouraging safety and efficacy with consolidation dosing [ASH abstract 649]. *Blood*. 2021;138(suppl 1).

Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. *Lancet Oncol*. 2019;20(1):31-42.

Locke FL, Miklos DB, Jacobson CA, et al; All ZUMA-7 Investigators and Contributing Kite Members. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. *N Engl J Med*. 2022;386(7):640-654.

Nastoupil LJ, Jain MD, Feng L, et al. Standard-of-care axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma: results from the US Lymphoma CAR T Consortium. *J Clin Oncol*. 2020;38(27):3119-3128.

Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med*. 2017;377(26):2531-2544.

Tilly H, Morschhauser F, Sehn LH, et al. Polatuzumab vedotin in previously untreated diffuse large B-cell lymphoma. *N Engl J Med*. 2022;386(4):351-363.

Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. *N Engl J Med*. 2020;382(14):1331-1342.