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The Role of CD-19 Targeting Chimeric Antigen Receptor (CAR) T-cell Therapy in Non-Hodgkin Lymphoma.

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Chimeric Antigen Receptor (CAR) T-cell therapy has improved outcomes in multiple hematological malignancies, such as multiple myeloma and non-Hodgkin lymphoma. CD-19 targeting CAR T-cells have improved outcomes in both aggressive and indolent types of non-Hodgkin lymphoma. Four CAR T-cell products have been approved by the United States (U.S.) Food and Drug Administration (FDA) for the management of non-Hodgkin lymphoma. This article reviews the currently available commercial CAR T-cells products' role in managing diffuse large B-cell lymphoma, follicular lymphoma, and mantle cell lymphoma. We summarize pivotal clinical trials and real-world data on their efficacy and safety.

INTRODUCTION

Chimeric Antigen Receptor (CAR) T-cell therapy has transformed the treatment landscape of hematological malignancies. Autologous CAR T-cell therapy is a form of personalized immunotherapy in which a patient's T-cells are genetically engineered to contain a CAR that recognizes a specific antigen in tumor cells. Several targets were identified for various cancers, but the two targets that showed the most success in clinical trials were CD19 and BCMA.[1] Two BCMA targeting CAR T-cells are approved by the United States (U.S.) Food and Drug Administration (FDA) for treating multiple myeloma and four CD19 targeting CAR T-cells are approved for treating some lymphoproliferative diseases.[2] Other targets are being investigated in various diseases, including T-cell and Hodgkin's lymphoma, solid tumors, and autoimmune diseases.[3-5]

The evidence of improved outcomes in several hematological malignancies with CAR T-cells makes it a promising and rapidly evolving immunotherapeutic agent. However, two important toxicities associated with CAR T-cell therapy include cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).[1, 6] CRS typically manifests shortly after CAR T-cell infusion with fevers, hypotension, and hypoxia in severe cases. Recognition of the target antigen by the CAR T-cells leads to a significant release of cytokines. It is typically treated with IL-6-directed therapy such as tocilizumab.[1,6]

Similarly, ICANS develops soon after infusion and can present with confusion, writing difficulty, motor deficits, seizures, and cerebral edema. It is treated supportively with corticosteroids.[1,6] Additionally, CAR T-cell therapy's long-term effects are still poorly understood, including the risk of subsequent malignancies.[7,8]

In this review, we summarize the current role of CAR T-cell therapy in the treatment of non-Hodgkin lymphoma, focusing on diffuse large B-cell, follicular, and mantle-cell lymphoma.

ROLE OF CD-19 CAR T-CELLS IN LARGE B-CELL LYMPHOMA

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL).[9] For newly diagnosed DLBCL, chemoimmunotherapy remains the mainstay of treatment, with R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone) and Pola-CHP (Polatuzumab vedotin, Cyclophosphamide, Doxorubicin, and Prednisone) as the standard regimens, achieving complete responses in majority of patients.[10-12] However, despite these therapies, a significant number of patients relapse or become refractory (R/R), which negatively impact their prognosis.[13]

Currently, three CD-19 CAR T-cell therapies are FDA-approved in the United States for the treatment of R/R

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DLBCL: Axicabtagene ciloleucel (axi-cel), Tisagenlecleucel (tisa-cel) and Lisocabtagene maraleucel (liso-cel).[2] Several landmark trials have evaluated the efficacy of these CD-19 CAR T-cell therapies in R/R DLBCL (see supplementary table 1). ZUMA-1 demonstrated an overall response rate (ORR) of 83% and a complete response (CR) rate of 58%, with a median OS of 25.8 months and a 5-year OS rate of 43%.[14,15] On the other hand, the JULIET trial and its follow up analysis evaluated tisa-cel in R/R DLBCL.[16,17] The primary study demonstrated an ORR of 52% and a CR rate of 40%. At a median follow-up of 40.3 months, 53% of patients maintained their response and 39% achieved a CR.[16,17]

Furthermore, the TRANSCEND-NHL-001 and PILOT trials evaluated liso-cel in R/R DLBCL patients across different settings. In the TRANSCEND trial, liso-cel achieved an ORR of 73% and a CR rate of 53% with a median OS of 27.3 months. The PILOT study, focusing on patients not eligible for HSCT, showed an ORR of 80% and a CR rate of 48%.[18-20]

Despite these promising results, CAR T-cell therapies are associated with significant toxicities, particularly CRS and ICANS. CRS is triggered by rapid immune activation and cytokine release, which can lead to hypotension and multiorgan failure in severe cases. In the ZUMA-1 trial, grade 3 or higher CRS was reported in 13%, while grade 3 or higher ICANS occurred in 28% of patients.[14] In the JULIET trial for tisa-cel, grade 3 or higher CRS occurred in 22% of patients, and neurological events occurred in 12%.[16] Liso-cel demonstrated a more favorable safety profile in the TRANSCEND NHL 001 trial, with grade 3 or higher CRS and ICANS rates of 2% and 10%, respectively.[19]

Additionally, multiple trial have investigated the role of CAR T-cell therapy in the second line setting, leading to two approvals for liso-cel and axi-cel after the Transform and ZUMA-7 trials.[21-23] ZUMA-7 evaluated axi-cel in the second-line setting in patients who had a primary refractory disease or relapsed within 12 months of their remission. It showed a significant improvement in event-free survival (EFS) compared to standard care, with a median EFS of 8.3 months vs 2.0 months, and higher ORR and CR rates.[21, 22]

Real-world studies have demonstrated the effectiveness and challenges of CAR T-cell therapy in R/R DLBCL, including among older patients.[24-26] For instance, in a multicenter analysis by Berning et al,[24] 172 patients were compared by age group (<70 vs. ⩾70 years). The study found similar ORR (77.7% vs. 78.3%) and progression-free survival (PFS-10.2 vs. 11.1 months), with no significant difference in grade ⩾3 CRS or neurotoxicity. Additionally, Bethge et al[25] conducted a real-world analysis of 356 patients from the German Registry for Stem Cell Transplantation, highlighting the impact of bridging therapy and CAR T-cell product selection on outcomes. Infections from prolonged neutropenia were identified as the main driver of non-relapse mortality (NRM), with higher NRM observed in patients treated with axi-cel. Elevated LDH, failed bridging therapy, and older age were significant risk factors for poor outcomes, emphasizing the importance of infection management and careful patient selection.

CD-19 CAR T-cell therapies have significantly impacted the treatment landscape for R/R DLBCL, offering new hope to a population with limited options. While the three main therapies—axi-cel, tisa-cel, and liso-cel—have shown robust efficacy in clinical trials, real-world data highlight the importance of infection management and long-term monitoring. Future research will be key in addressing current limitations and expanding the role of CAR-T cells in DLBCL treatment.

ROLE OF CD-19 CAR T-CELLS IN FOLLICULAR LYMPHOMA

Follicular lymphoma (FL) is considered an incurable, indolent type of non-Hodgkin lymphoma with a relapsing and remitting course.[27] FL is the second most diagnosed B-cell lymphoproliferative disease in the United States and Western Europe that is commonly detected at an advanced stage. Despite being highly responsive to early lines of treatment, approximately 20% of patients with FL experience relapse within 2 years of treatment.[28] In the past two decades, there have been many advancements in treatment options that have improved the median overall survival of patients with FL.

CAR T-cells have increased the treatment options particularly for FL patients with relapsed/refractory (r/r) disease after >2 lines of treatment. Currently, there are several CAR T-cells approved by the U.S. FDA for the treatment of r/r FL including: Axi-cel, tisa-cel and liso-cel (see supplementary table 2).

In the phase 2, multicenter, single-arm, ZUMA-5 study,[29] 124 adult patients with histologically confirmed r/r FL received axi-cel. In the primary analysis by Jacobson et al., out of 127 patients, axi-cel resulted in an ORR in 119 (94%) patients and CR rate in 100 (79%) patients. At the three-year follow-up analysis, the median PFS was 40.2 months and the median overall survival (OS) was not reached.[30] Grade 3 or worse CRS occurred in eight (6%) patients and grade 3 or 4 neurological events occurred in 19 (15%) patients.[29] This trial indicated a favorable response in patients that were overall considered high risk (failed >2 prior lines of therapy).

The ELARA trial was a single-arm phase 2, multinational trial that used tisa-cel, another autologous anti-CD19 CAR T-cell therapy.[31,32] The study enrolled 97 patients with r/r FL who had undergone two or more lines of therapy. In the primary analysis, ORR was 86% with a CR rate 69%. With a median follow-up of 17 months, median PFS and OS were not reached. Longer-term analysis revealed that an estimated 24-month PFS rate in all patients was 57.4% and OS rate was 87.7%. Rates of Grade 3 CRS was 0% and grade >3 ICANS was 1%.[31,32] These studies showed tisa-cel has comparable efficacy with favorable safety outcomes than axi-cel[33] and can be administered in an outpatient setting.[31,32]

Liso-cel is the third approved CD19.CAR T-cell after the phase 2 TRANSCEND FL trial.[34] It evaluated the use of liso-cel as second line treatment in 23 patients with r/r FL who had high-risk disease features such as progression of disease within 24 months and 107 patients as third line treat-

ment or later (3L+). The TRANSCEND FL trial evaluated CAR-T in the largest population to date and revealed a similar efficacy profile with median PFS and OS not reached at a median follow-up of 17.8 months. The 12-month PFS rate was 91%, and 12- month OS rate was 96%.[34] It also had a similar safety profile as Grade 3 CRS occurred in 1% of patients and neurological events grade 3 or greater occurred in 2% of patients.

ROLE OF CD-19 CAR T-CELLS IN MANTLE CELL LYMPHOMA

Mantle cell lymphoma (MCL) is a less common type of NHL, with clinical manifestations ranging from asymptomatic cases to extra-nodal involvement, affecting numerous organ systems, such as the gastrointestinal tract and central nervous system.[35] The role of CD-19 CAR T-cells in the treatment of refractory or relapsed Mantle cell lymphoma was established by the ZUMA-2 and TRANSCEND NHL 001 early phase trials leading to the approval of two CAR T-cell products by the U.S. FDA (refer to supplementary table 3).[36,37]

ZUMA-2 is a multi-center, single-arm phase 2 clinical trial that evaluated the efficacy and safety of Brexucabtagene autoleucel (Brexu-cel) in patients with relapsed/refractory MCL.[35] Brexu-cel is a second-generation CD-19 targeting CAR T-cell. The trial enrolled 74 patients, but brexu-cel was administered to 68 heavily pretreated MCL patients, 37% of whom received bridging therapy. Patients received a median of 3 (range, 1-5) prior lines of therapy with 81% of patients receiving 3 or more lines of therapy. The primary endpoint of the trial was ORR. There were multiple additional secondary endpoints including DOR, PFS and OS.[36] In the most recent analysis of ZUMA-2 with a median follow-up of 35.6, ORR of 91%, with 68% achieving a CR. The median duration of response was reported to be 28.2 months with a reported median PFS of 25.8 months and median OS of 46.6 months. The 24 months PFS was 53% and the 30 months OS was 60%.[38] Most patients (91%) experienced CRS; grade 3 or higher CRS occurred in 15% of patients. ICANS events were reported in 63% of patients with 31% of patients with grade 3 or higher. Most adverse events were effectively managed with tocilizumab and glucocorticoids. The median time to adverse event resolution was 11 days. The most frequently reported grade $\geq$ 3 adverse event was cytopenia.[36]

More recently, results of the analysis of the MCL cohort of the TRANSCEND NHL 001 trial were published. TRANSCEND NHL 001 is a phase 1 open-label trial evaluating the safety and efficacy of lisocabtagene maraleucel (liso-cel) in different NHL patients.[37] The study recruited 104 MCL patients, who had been exposed to $\geqslant$ 2 prior lines of therapy, including BTK inhibitors; 88 received liso-cel infusion.[37] The efficacy set of 83 patients reported an ORR of 83.1%, with 72.3% achieving a CR. Patients with high-risk features had similar responses. CR rates were higher when compared to the ZUMA-2 study. Median DOR was 15.7 months (28.2 in the ZUMA-2 study). Median PFS and OS were 15.3 and 18.2 months, respectively. Adverse events of grade 3 or higher were observed in 86% of patients, mostly cytopenia. CRS of all grades occurred in 61% of patients; only 1% experienced a grade 3 or higher CRS, grade 4 specifically. ICANS occurred in 31% of patients; 9% had grade 3 or higher. Approaches to manage toxicities were the same in both trials.[37]

Additionally, real-world data confirms the notable efficacy and safety of CD-19 targeting CAR T-cell therapy in relapsed/refractory MCL. However, all currently published studies are utilizing brexu-cel. The largest real-world study results investigating brexu-cel, which included a distinct population that wasn't included in ZUMA-2, were published by the US Lymphoma CAR T Consortium, affirming the treatment's efficacy and safety.[39] 168 r/r MCL patients received brexu-cel. ORR was 90%, with 82% achieving CR. With a median follow-up of 14.3 months, Median DOR was 17.2 months, whereas median PFS was 16.4 months. Median OS wasn't reached but at 1-year estimation it was 75%. High risk features were common, as 68% received bridging therapy (compared to 37% in ZUMA-2) and 10% had CNS involvement. Similar safety profile was observed compared to the ZUMA-2 study, CRS and ICANS of grade 3 or higher occurred in 8% and 32%, respectively.[38] These results were supported by smaller studies. For instance, Lacoboni et al.[40] reported the results of 33 r/r MCL patients who received brexu-cel, at a median follow-up of 10.1 months. Similar efficacy and safety results were observed.[39] Furthermore, in a multi-center study in the UK,[41] 83 r/r MCL patients, who had been exposed to a median of 2 previous lines of therapy, received brexu-cel. 90% of patients received bridging therapy after leukapheresis, reflecting a population at a higher risk than the ones seen in the other real-world studies. Following a median follow-up of 13.3 months, ORR was 87%, with 81% achieving CR, while these rates are slightly lower compared to other studies, this emphasized the efficacy of brexu-cel in high-risk populations. The median PFS was 21 months. Median OS was not reached but, 1-year estimated OS was 74%. High-risk factor subgroups were associated with less favorable survival outcomes. Grade $\geq$3 CRS and ICANS were reported in 12% and 22%, respectively.[41]

Ahmed et al.[42] reported on brexu-cel use in a population of 12 r/r MCL patients with CNS involvement, a characteristic that was also present in the US Consortium study but excluded from landmark trials. Eleven of these patients received brexu-cel, while one patient received an investigational therapy targeting both CD-19 and CD-20. Among those, eight had active CNS disease at the time of lymphodepletion, and the rest did not have active CNS disease at the time of infusion. Six (50%) patients received bridging therapy; 2 patients had cranial radiation as bridging therapy to help control CNS disease, an approach that is not observed in other RWE studies.[42] Promising efficacy was observed; at 3 months, CNS response and ORR were the same, as 92% achieved CR. PFS and OS at 1 year for patients with active CNS disease were 25% and 63%, respectively. Although these outcomes were lower compared to other studies, patients in this study were at a higher risk. No grade 3 or higher CRS was reported. ICANS of grade 3 or higher

occurred in 58%, which is higher compared to the ZUMA-2 study.[42]

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SUPPLEMENTARY MATERIALS

Supplementary material

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