Literature review

The current role of autologous stem-cell transplantation in relapsed/refractory diffuse large B-cell lymphoma in the CAR-T therapy era

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Introduction

Diffuse Large B-cell Lymphoma (DLBCL) is the most common form of non-Hodgkin lymphoma (NHL) globally, accounting for approximately 22% of newly diagnosed B-cell NHL cases in the United States. Its incidence increases with age, peaking in the mid-60s, with 30% of patients over the age of 75.[1] DLBCL represents a heterogeneous group of morphologically, genetically and clinically distinct diseases. Among its aggressive subtypes, DLBCL, not otherwise specified (NOS), is the most prevalent. Notably, DLBCL/high-grade B-cell lymphoma (HGBCL) with *MYC* and *BCL2* rearrangements has been recognized as a distinct entity due to its unique and uniform gene expression profile.[2]

Most cases of DLBCL (50-70%) can be cured with the immunochemotherapy regimen of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP).[3,4] However, 30-40% of newly diagnosed DLBCL patients experience relapse or progression, typically within the first two years. While some relapsed patients can be cured with secondary therapies, the majority succumb to the disease. Additionally, 10-15% of patients present with primary refractory disease, characterized by incomplete response or relapse within 3 to 6 months. These patients often exhibit inherent chemotherapy resistance and have the poorest outcomes with a median overall survival (OS) of approximately six months. Patients experiencing late relapses, beyond two years, may have more favorable outcomes, suggesting a biologically distinct form of the disease.

Autologous Stem-cell Transplantation (auto-HSCT) for Relapsed DLBCL

The standard second-line treatment for relapsed or refractory (R/R) DLBCL in the curative setting is high-dose chemotherapy followed by autologous stem-cell transplantation (auto-HSCT). The PARMA trial, conducted in 1995, established the role of auto-HSCT in patients with chemosensitive relapse.[5] In this randomized trial, 109 patients with chemosensitive disease were assigned to receive either four cycles of chemotherapy using the dexamethasone, high-dose cytarabine and cisplatin (DHAP) regimen (n = 54) or auto-HSCT (n = 55). With a median follow-up of 63 months, the OS rate for auto-HSCT was superior (84% vs. 44%). At five years, the OS rate was 53% for the auto-HSCT group vs. 32% in the control group, and the event-free survival (EFS) rate was also significantly higher (46% vs. 12%). This trial confirmed auto-HSCT as the standard of care for chemosensitive relapsed DLBCL, although the trial focused on patients aged ≤ 60 years.

However, certain disease characteristics, such as primary refractoriness, a high second-line age-adjusted International Prognostic Index (IPI) and HGBCL with double- or triple-hit genetic lesions, are associated with lower response rates to auto-HSCT.

In the postrituximab (post-R) era, the CORAL trial[6] comparing R-DHAP and R-ICE (rituximab, ifosfamide, carboplatin and etoposide), identified a poor risk population: patients with prior exposure to rituximab and those with R/R disease within 12 months of diagnosis. For

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these patients, the three-year progression-free survival (PFS) was only 23%. Similarly, the LY.12 trial,[7] comparing DHAP with GDP (gemcitabine, dexamethasone, cisplatin), demonstrated poor outcomes in patients with primary refractory disease or an initial response duration of less than 12 months. In the CORAL trial,[6] patients with R/R DLBCL, receiving third-line chemotherapy, showed a response rate of 39%, with 27% achieving complete remission (CR) and 12% partial remission (PR). Among the 203 patients, 64 (31.5%) underwent transplantation (56 auto-HSCT and 8 allogeneic HSCT). The median OS for the entire population was 4.4 months. Patients responding to third-line treatment and subsequently undergoing transplantation had a one-year OS of 41.6%, compared with 16.3% for those not transplanted ($p < 0.0001$). These findings suggest that third-line salvage chemotherapy can yield responses that enable auto-HSCT and long-term survival in some patients with R/R DLBCL. However, there remains an urgent need to improve the efficacy of salvage regimens with newer drugs.

The SCHOLAR-1 study,[8] an international multicohort retrospective analysis of NHL, evaluated outcomes in patients with refractory DLBCL, defined as progressive or stable disease at any point during chemotherapy (more than four cycles of first-line or two cycles of later-line therapy) or relapse within 12 months of auto-HSCT. Among 861 patients, 636 met the inclusion criteria for refractory disease. For these patients, the objective response rate to the next line of therapy was 26% with a CR rate of 7%. The median OS was 6.3 months, and 20% of patients were alive at two years. With standard second-line regimens such as R-ICE or R-DHAP followed by auto-HSCT in responding patients, the expected three-year EFS in the post-R era is only 20%. Outcomes are especially poor for patients with primary refractory disease or those who relapse within 12 months of initial treatment groups accounting for nearly two-thirds of R/R DLBCL cases. These poor outcomes emphasize the need for novel therapeutic options in this setting.

In the post-R era, the benefit of auto-HSCT appears to be diminished, particularly for patients with refractory or early relapsing disease, representing the majority of cases. Moreover, many patients are not fit for auto-HSCT, and up to one-half are chemo-resistant, rendering auto-HSCT an unsuitable option. Until recently, no established therapy existed for patients with R/R DLBCL beyond second-line treatment. As a result, pilot trials have begun evaluating chimeric antigen receptor (CAR) T-cell therapy as a third-line treatment for R/R DLBCL.

Chimeric Antigen Receptor T-Cell Therapies (CAR T-Cell)

CAR T-cell therapies targeting CD19 have revolutionized the treatment of multiply relapsed DLBCL, showing promising rates of durable remission in up to 40% of patients, including those with refractory disease.[9-11] CAR T-cell therapy is a multistep process involving leukapheresis to collect the patient's T cells, gene modification to introduce the CAR construct, ex vivo expansion and infusion of the CAR T cells after the patient receives lymphodepleting chemotherapy. This process can take several weeks, making it challenging for patients with rapidly progressing or bulky disease, who may require bridging therapy before infusion.

Three CD19-targeting CAR T-cell therapies have been approved for third-line treatment of DLBCL based on pivotal phase 2 studies: Axicabtagene ciloleucel (Axi-cel),[10] Tisagenlecleucel (Tisa-cel)[9] and Lisocabtagene maraleucel (Liso-cel).[11] Despite differences in costimulatory domains (CD28 for Axi-cel vs. 4-1BB for Tisa-cel and Liso-cel) and gene transfer methods (retrovirus for Axi-cel vs. lentivirus for Tisa-cel and Liso-cel), these products have demonstrated similar efficacy and toxicity profiles. Below is a summary of the key studies for each therapy.

Axicabtagene Ciloleucel (Axi-cel):

Axi-cel, an autologous anti-CD19 CAR T-cell therapy, was approved by the US FDA on October 18, 2017, for

treating adults with R/R DLBCL, primary mediastinal large B-cell lymphoma (PMBCL), transformed follicular lymphoma (tFL) and HGBCL after the failure of at least two prior systemic therapies. In the ZUMA-1 trial,[10] 111 patients were enrolled, with 110 (99%) successfully manufacturing Axi-cel, and 101 (91%) receiving the infusion. The median age was 58 years, and most patients had advanced-stage disease with at least three prior lines of therapy. The overall response rate (ORR) was 82%, with 54% CR. At a median follow-up of 15.4 months, 42% of patients maintained a response, and 40% remained in CR. The 18-month OS was 52%. Common grade 3 or higher adverse events included neutropenia (78%), anemia (43%), thrombocytopenia (38%), cytokine release syndrome (CRS) (13%) and neurological events (28%). Axi-cel demonstrated high levels of durable response but was associated with notable side effects, including myelosuppression, CRS and neurological events.[12]

Tisagenlecleucel (Tisa-cel):

The JULIET trial,[9] a global, multicenter, open-label phase 2 study, evaluated Tisa-cel in 111 adult patients with R/R DLBCL ineligible for, or experiencing progression after, auto-HSCT. The median age was 56 years, and 49% of patients had prior auto-HSCT. The ORR was 52% with 40% achieving CR and 12% achieving PR. At 12 months, the relapse-free survival rate was 65%, and among those in CR, 79% were relapse-free. Common grade 3 or 4 adverse events included CRS (22%), neurological events (12%), prolonged cytopenias (32%), infections (20%) and febrile neutropenia (14%). After a median follow-up of 40.3 months, the OS rate was 53%, with 39% of patients achieving CR as their best overall response. Tisa-cel demonstrated durable activity with a manageable safety profile.

Lisocabtagene Maraleucel (Liso-cel):

The TRANSCEND-NHL-001 phase 1/2 trial[11] conducted across 14 cancer centers in the USA enrolled 344 patients with R/R DLBCL, HGBCL (double- or triple-hit), tFL, PMBCL and FL grade 3B. Of these, 269 patients received at least one dose of Liso-cel. The median age was 63 years with 67% having chemotherapy-refractory disease and 3% having secondary CNS involvement. The ORR was 73% with 53% achieving CR. Grade 3 or higher adverse events included neutropenia (60%), anemia (37%), thrombocytopenia (27%), CRS (42%) and neurological events (30%). Liso-cel demonstrated a high response rate with a relatively low incidence of severe CRS and neurological events, even in patients with diverse histological subtypes and high-risk features.

All three CAR T-cell therapies - Axi-cel, Tisa-cel and Liso-cel - have demonstrated significant response rates and durable remissions in approximately 40% of treated patients. These therapies are now FDA-approved for patients with R/R DLBCL after at least two lines of therapy, providing hope for patients previously having limited treatment options.

CAR T-Cell Toxicity

The toxicity profiles of the three major CAR T-cell therapies are summarized in Table 2. Despite similar overall toxicity profiles, differences were noted in the incidence of certain adverse events. Grade 3 or higher CRS was observed in 23% of patients receiving Tisa-cel, compared with 11% with Axi-cel and 2% with Liso-cel. Axi-cel was associated with the highest rate of grade 3 or higher neurotoxicity at 32%, while Tisa-cel and Liso-cel had rates of 10-12%.

Phase 3 Trials for CAR T-Cell Therapies vs. Auto-HSCT (Standard of Care)

Building on the promising results from phase 2 pivotal trials and favorable comparisons with standard of care (SOC) outcomes in the CORAL and LY.12 trials, it was hypothesized that CAR T-cell therapy could achieve superior outcomes compared with salvage chemotherapy followed by auto-HSCT as second-line therapy in patients with high-risk relapsed/refractory DLBCL. To test this hypothesis, three randomized phase 3 trials were launched: ZUMA-7 (Axi-cel),[13] BELINDA (Tisa-cel)[14] and TRANSFORM (Liso-cel).[15] The results of these trials are summarized in Table 3.

Table 1 Updated of Outcomes from the Pivotal CAR T phase 2 trials approved by US Food and Drug Administration[9-11]

	Axi-cel	Tisa-cel	Liso-cel
CAR T construct	CD19.28.CD3z	CD19.44BB.CD3z	CD19.44BB.CD3z
Source	Fresh unsorted PBMCs	Cryopreserved unsorted PMBCs	Fresh Sorted PMBCs
Pivotal trial	ZUMA-1	Juliet	Transform
Most mature follow-up (months)	63.1	40.3	24
Median duration of response (months)	11.1	NE	23.1
ORR/CR (%)	83/58	52/39	73/53
Median PFS (months)	5.9	2.9	6.8
PFS, 24 months (%)	36	33	40.6
Median OS (months)	25.8	11.1	27.3
OS, 24 months (%)	50.5	40	50.5
CRS: Any/Grade3+ (%)	93/13	57/23	42/2
Neuro Toxicity Any/Grade 3+ (%)	64/28	20/11	30/10

CR = complete remission; CRS = cytokine release syndrome; PBMCs = peripheral blood mononuclear cells; PFS = progression-free survival; ORR = overall rate; OS = overall survival

Table 2 Summary of Toxicity of the 3 Major CAR T -cell Treatment in 3L Refractory/Relapse DLBCL[9,10,11]

	Axi-cel	Tisa-cel	Lisa-cel
Construct	antiCD19-CD28-CD3z	antiCD19-41BB-CD3z	antiCD19-41BB-CD3z
Number	101	111	269
Any CRS	93%	58%	42%
Median time to onset	2 days	3 days	5 days
≥ Grade 3 CRS	11%	23%	2%
Any Neurotoxicity	64%	21%	30%
≥ Grade 3 Neurotoxicity	32%	12%	10%
Tocilizumab	43%	15%	20%
Steroid Use	27%	11%	21%

CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma

ZUMA-7 (Axi-cel)

The ZUMA-7 international phase 3 trial enrolled 359 patients with a median age of 58 years (range 21-80).[13] The primary endpoint analysis of EFS demonstrated that Axi-cel was superior to SOC. At a median follow-up of 24.9 months, the median EFS was 8.3 months in the Axi-cel group compared with 2.0 months in the SOC group. The 24-month EFS rates were 41% for Axi-cel and 16% for SOC. In an interim analysis, the estimated 2-year OS was 61% for Axi-cel vs. 52% for SOC. At a further median follow-up of 47.2 months, the median OS was not reached in the Axi-cel group and was 31.1 months for SOC, with estimated 4-year OS rates of 54.6% and 46.0%, respectively (p = 0.03).[12] The median PFS was 14.7 months in the Axi-cel group compared with 3.7 months for SOC with a 4-year PFS rate of 41.8% vs. 24.4%. This trial showed that Axi-cel therapy led to significant improvements in EFS, PFS and OS compared with standard care, making it a preferred second-line treatment for patients with early R/R DLBCL.

Table 3 Results of Phase 3 Trials of CAR T-cell Therapies vs. Standard of Care 2L Transplant-eligible Diffuse Large B-cell Lymphoma with Primary Refractory Disease or Relapse within 12 months of 1L

	ZUMA-7	TRANSFORM	BELINDA
Car T-cell product	Axi-cel	Liso-cel	Tisa-cel
CAR construct	CD19.CD28.CD3z	CD19.41BB.CD3z	CD19.41BB.CD3z
#Enrolled	359	184	322
Stratified Randomization	1L Response/ 2L aaIPI	1L Response/ 2L aaIPI	1L DoR/IPI/Region
Timing of CAR T leukapheresis	After randomization	At enrollment	At enrollment
Bridging Treatment Allowed	Yes	Yes	Yes
	Steroid only	Investigator-choice PCIT	Investigator-choice PCIT
LD Chemotherapy	Flu/Cy	Flu/Cy	Flu/Cy or Bendamustine
SOC Crossover allowed	Off protocol	Yes	Yes (after 2 different PCIT)
Median Age (range)	58 (21-80)	60 (20-74)	60 (19-79)
Median Follow Up	24.9 months	6.2 months	10 months
Received Bridging in CAR T arm (%)	36%	63%	83%
To HSCT in SOC arm (%)	36%	47%	33%
SOC Crossover to CAR T (%)	56%	55%	51%
Median EFS	8.3 vs 2 months	10.1 vs 2.3 months	3 vs 3 months
Hazard Ratio	0.398 ($p < 0.0001$)	0.349 ($p < 0.0001$)	1.07 ($p = 0.69$)
CR Rate	65% vs 32%	66% vs 39%	28% vs 28%
PFS, median	14.7 vs 3.7 months	14.8 vs 5.7 months	NR/NR
Grade ≥ CRS/ICANS	6%/21%	1%/4%	5%/3%

Cy = Cyclophosphamide; CR = complete remission; CRS = cytokine release syndrome; EFS = Event-free survival; Flu = fludarabine; HSCT = hematopoietic stem cell transplantation; ICANS = immune effector cell-associated neurotoxicity syndrome; LD = low-dose; NR = not reported; PFS = progression-free survival; SOC = standard of care

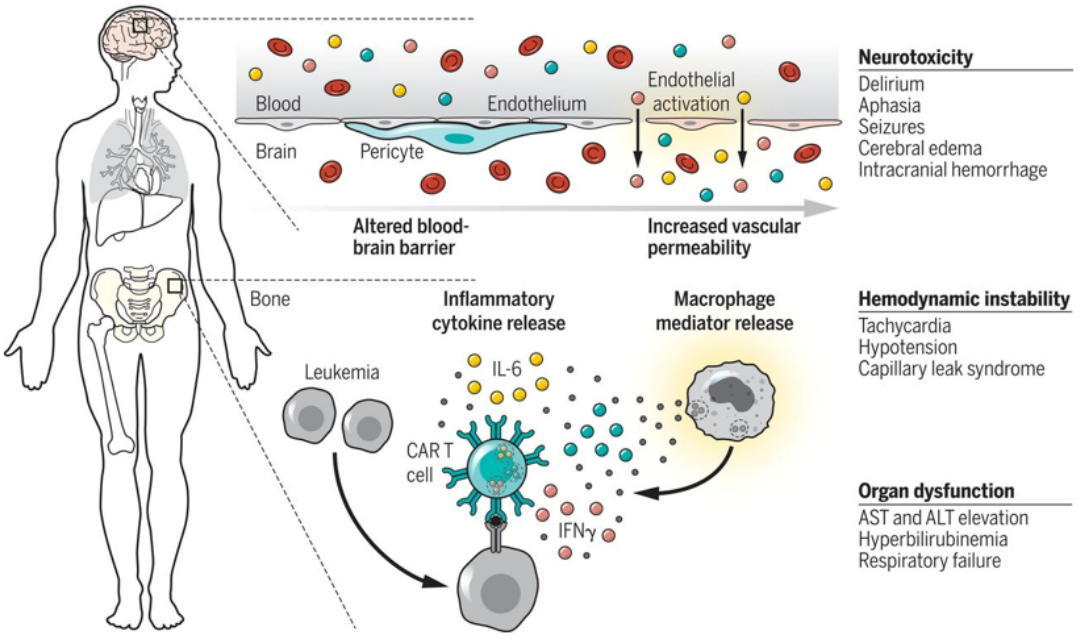

Figure 1 Mechanisms of Acute Toxicity in CAR T-cell Therapy (adapted from June CH, et al. Science. 2018;359:1361-5.)

BELINDA (Tisa-cel)

The BELINDA international phase 3 trial enrolled 322 patients.[14] The percentage of patients with HGBCL was higher in the Tisa-cel group than in the SOC group (24.1% vs. 16.9%), as was the percentage with an age-adjusted IPI score of 2 or higher. A total of 95.7% of patients in the Tisa-cel group received the infusion, compared with 32.5% of patients in the SOC group undergoing auto-HSCT. The median time from leukapheresis to Tisa-cel infusion was 52 days. By week 6, 25.9% of patients in the Tisa-cel group experienced disease progression, compared with 13.8% in the SOC group. Both groups had a median EFS of 3.0 months (p = 0.61) with ORR of 46% for Tisa-cel and 43% for SOC. In total, 51% of patients in the SOC group crossed over to receive Tisa-cel. The reasons for the lack of superiority in the Tisa-cel group included prolonged time to infusion, a higher percentage of patients with HGBCL and high IPI scores and the overall lower efficacy of Tisa-cel in this setting. Tisagenlecleucel did not demonstrate superiority over SOC in this trial.

TRANSFORM (Liso-cel)

The TRANSFORM global phase 3 study compared Liso-cel with SOC as second-line therapy for patients with primary refractory or early relapsed (≤ 12 months) DLBCL.[15] A total of 184 adults eligible for auto-HSCT were randomly assigned in a 1:1 ratio to receive Liso-cel or SOC. The median age was 60 years (range 20-75). Bridging chemotherapy was administered to 63% of patients in the Liso-cel group, and 97.8% received the CAR T-cell infusion. In contrast, only 45.6% of patients in the SOC group underwent auto-HSCT. In the primary analysis with a median follow-up of 17.5 months, the median EFS was not reached (NR) for Liso-cel vs, 2.4 months for SOC. The CR rate was significantly higher in the Liso-cel group (74%) compared with SOC (43%) (p < .0001), and the median PFS was also NR for Liso-cel compared with 6.2 months for SOC (p < .0001). Median OS was NR for Liso-cel vs. 29.9 months for SOC (p = .0987). After adjusting for crossover, the 18-month OS rates were 73% for Liso-cel and 54% for SOC. These data suggest that Liso-cel provides significant improvements in EFS, CR rate and PFS, making it a preferred second-line treatment for patients with primary refractory or early relapsed DLBCL.

Safety and Efficacy of Axi-cel vs. Standard of Care in Patients 65 Years or Older with Relapsed/Refractory Large B-Cell Lymphoma

A preplanned subgroup analysis from the ZUMA-7 trial evaluated outcomes in patients aged ≥ 65 years, with 51% of patients randomized to receive Axi-cel and 58% to SOC.[16] The median EFS was significantly longer with Axi-cel compared with SOC (21.5 vs. 2.5 months; median follow-up: 24.3 months; p < 0.0001). The objective ORR was higher with Axi-cel than with SOC (88% vs. 52%; p < 0.0001), and the CR rate was 75% vs. 33%, respectively. Grade 3 or higher adverse events occurred in 94% of Axi-cel patients and 82% of SOC patients, with no grade 5 CRS or neurologic events reported. In a quality-of-life analysis, patient-reported outcomes at days 100 and 150 favored Axi-cel over SOC for EORTC QLQ-C30 Global Health, Physical Functioning, and EQ-5D-5L visual analog scale (p < 0.05). CAR T-cell expansion and baseline serum inflammatory profiles were comparable between patients aged ≥ 65 and those under 65 years. These results support Axi-cel as an effective second-line, curative-intent therapy with a manageable safety profile and improved quality of life for patients aged ≥ 65 years with R/R DLBCL.

Liso-cel as Second-Line Therapy in Adults with R/R DLBCL Who Were Not Candidates for Auto-HSCT (PILOT Study)

The PILOT phase 2 study, conducted at 18 clinical sites in the USA, evaluated Liso-cel as second-line therapy for adults with R/R DLBCL who were not candidates for HSCT due to age, performance status or comorbidities, regardless of the time to relapse.[17] The median age of

patients was 74 years (IQR 70-78), with 26% having an ECOG performance status of 2, 54% presenting with refractory disease, 21% relapsing within one year of first-line therapy and 25% relapsing after 12 months. With a median follow-up of 12.3 months, 54% of patients achieved a CR, the median PFS was 9 months, and the median OS was not reached. These findings support Liso-cel as a viable second-line treatment option for patients with DLBCL, who are not candidates for auto-HSCT due to advanced age or other factors.

CAR T-Cell Therapy as Third-Line or Later

Three autologous CD19-directed CAR T-cell therapies - Axi-cel, Tisa-cel and Liso-cel - are approved for adult patients who have failed at least two lines of therapy, based on single-arm phase II studies.[9-11] These studies demonstrated that 35-40% of patients with relapsed/refractory DLBCL in the third-line or later setting may be cured, representing a significant improvement over the 6-month survival previously observed among similar patients before CAR T-cell therapy was available. Despite the promising outcomes of these prospective studies and comparable findings with commercial products,[18] CAR T-cell therapy remains underutilized, likely due to factors such as limited access and rapidly progressing disease that precludes waiting for manufacturing, and resource demands.

Real-World Study of Liso-cel in Patients with R/R DLBCL in the United States

A real-world study evaluated the outcomes of 323 patients with R/R DLBCL treated with Liso-cel using data collected by the Center for International Blood and Marrow Transplant Research (CIBMTR) between February 2021 and November 2022.[19] The median age was 70 years (range, 24-91), with most patients having DLBCL NOS (81%). Additionally, 27% had tFL, 12% had HGBCL, 37% had an IPI score of ≥ 3, 6% had active CNS involvement, and 15% had undergone prior transplantation. The median number of prior lines of systemic therapy was 3 (range, 0-11), with 25% having received ≥ 4 lines. At a median follow-up of 7.4 months, the ORR was 79%, with a 65% CR rate. The median time to response was 1.2 months (IQR, 1.0-3.1), and the median duration of response had not been reached; the 6-month duration of response was 73% (95%CI: 66-79%). Estimated 6-month PFS and OS rates were 64 and 82%, respectively. Most CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) events were low-grade. These results demonstrate that Liso-cel provides deep and durable responses in patients with R/R DLBCL across a broad age range, including those with high-risk features typically associated with poor prognosis, supporting its use as a therapeutic option with a favorable benefit/risk profile.

Outcomes of Outpatient CAR T-Cell Therapy in Non-Hodgkin Lymphoma

Given the potentially life-threatening toxicities of CAR T-cell therapy, such as CRS and ICANS, inpatient infusion and monitoring are often recommended. However, patients with R/R DLBCL have been successfully treated with Liso-cel and monitored for toxicity in outpatient settings across various sites.[20] Severe CRS, neurotoxicity and early hospitalization rates were low, with 43% of patients not requiring hospitalization. In another study of outpatient Tisa-cel administration at a US multicenter consortium, 157 patients were evaluated, with 93 (57%) receiving outpatient treatment and 64 (43%) inpatient treatment.[21] The incidences of any-grade CRS and ICANS were lower in the outpatient group (29% vs. 56%, $p < .001$; and 10% vs. 16%, $p = .051$, respectively). Unplanned admissions were required for 42 outpatient Tisa-cel recipients (45%), with a median 5-day length of stay (range, 1 to 27), compared with 13 days (range, 4 to 38) in the inpatient group. No toxicity-related deaths occurred within 30 days post-CAR T-cell infusion in either group. PFS and OS were similar between the two groups. With appropriate patient selection, outpatient Tisa-cel administration is feasible and can yield similar efficacy outcomes to inpatient treatment, while optimizing healthcare resource utilization.

Autologous Transplant vs. CAR-T Therapy in Patients with Relapsed DLBCL in Complete Remission

For patients with relapsed DLBCL in CR, both auto-HSCT and CAR T-cell therapy are effective treatment options. However, the question of which modality provides superior outcomes remains unresolved. A retrospective observational study using the CIBMTR registry compared auto-HSCT (2015-2021) with CAR T-cell therapy (2018-2021) in patients with DLBCL in CR at the time of treatment.[22] The median follow-up was 49.7 months for the auto-HSCT cohort and 24.7 months for the CAR-T cohort. Patients receiving only one prior line of therapy for auto-HSCT and those with a history of prior auto-HSCT in the CAR-T cohort were excluded. Univariate analysis revealed that auto-HSCT was associated with a higher two-year PFS (66.2% vs. 47.8%, p <0.001), a lower two-year cumulative incidence of relapse (27.8% vs. 48%, $p < 0.001$), and a superior two-year OS (78.9% vs. 65.6%, $p = 0.037$). Among patients with early treatment failure (within 12 months), auto-HSCT was associated with a superior two-year PFS (70.9% vs. 48.3%, $p < 0.001$), a lower relapse rate (22.8% vs. 45.9%, $p < 0.001$), and a trend toward higher two-year OS (82.4% vs. 66.1%, $p = 0.076$). Multivariable analysis confirmed that auto-HSCT was associated with better PFS (HR 1.83, $p = 0.0011$) and a lower relapse rate (HR 2.18, $p < 0.0001$) compared with that of CAR-T. These data suggest that among patients with relapsed DLBCL achieving CR, auto-HSCT may provide superior outcomes compared with CAR-T, supporting its consideration in select cases.

Autologous Transplant vs. CAR T-Cell Therapy for Relapsed DLBCL in Partial Remission

A study using the CIBMTR registry compared outcomes among adult patients with DLBCL in PR by CT or PET scan and treated with either auto-HSCT (2013-2019) or Axi-cel CAR-T therapy.[23] Univariable analysis showed no significant difference in two-year PFS (52% vs. 42%, $p = .51$) or 100-day non-relapse mortality (NRM) (4% vs. 2%, $p = .3$) between the two groups. However, auto-HSCT was associated with a lower relapse rate (40% vs. 53%, $p = .05$) and superior two-year OS (69% vs. 47%, $p = .004$). Multivariable regression confirmed that auto-HSCT was associated with a significantly lower risk of relapse ($p = .01$) and superior OS ($p = .008$) compared with that of CAR-T. These findings support the role of auto-HSCT as the standard of care for transplant-eligible patients with relapsed DLBCL in PR after salvage therapy.

CAR T-Cell Toxicities[24]

CRS is a common and potentially life-threatening toxicity observed with CAR T-cell therapies targeting CD19. When CAR T cells engage with their target antigens, they release a variety of cytokines and chemokines. Additionally, macrophages and other cells of the innate immune system become activated, further contributing to the release of soluble mediators. CAR T cells have been detected in cerebral spinal fluid, and these cytokines can increase vascular permeability, allowing more CAR T cells and other lymphocytes to traffic to the central nervous system. CRS is characterized by elevated levels of cytokines such as interleukin (IL)-6 and interferon γ. Studies have shown that immunosuppression with tocilizumab (an anti-IL-6 receptor antibody), with or without corticosteroids, can reverse the syndrome. However, early and aggressive immunosuppression may limit the efficacy of the therapy. Therefore, treatment algorithms are based on the severity of CRS among individual patients. Notably, CRS severity tends to be greater among patients with a higher disease burden. Incorporating immunotherapy in regimens for patients with lower disease burdens may reduce the incidence of CRS and improve outcomes without clinical evidence of toxicity.

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Neurotoxicity, known as ICANS, is another frequent and acute toxicity observed in up to 64% of CAR T-cell clinical trials.[25] While CRS is a known side effect of T-cell immunotherapy, unexpected neurologic complications ranging from mild to life-threatening have also been reported with CAR T-cell therapies targeting CD19 and B-cell maturation agent (BCMA). These neurotoxicities are largely reversible, and evidence suggests that endothelial injury, possibly driven by inflammatory cytokines, plays a role in the onset of neurotoxicity. However, the precise mechanisms underlying T-cell immunotherapy-mediated CRS and cerebral edema remain poorly understood. High-grade ICANS is more common in CAR T-cells using CD28 as the costimulatory domain, with rates of up to 45%. In contrast, CAR T-cells using 4-1BB costimulatory domains, such as Tisa-cel, show lower rates of severe ICANS with incidence rates up to 13%.

Late CAR T-Cell Toxicities

Late toxicities of CAR T-cell therapy, beyond the acute phase include cytopenias, hypogammaglobulinemia and an increased susceptibility to infections including bacterial, fungal and viral infections, as well as reactivation of latent viruses.

Potential Link between CAR T-Cell Therapy and Secondary Tumors

An emerging concern with CAR T-cell therapy is the risk of secondary malignancies, particularly T-cell neoplasms potentially related to viral vector integration. Data from two institutions, along with reports from the FDA, have raised awareness of this issue.[26-28] At the University of Pennsylvania, the incidence of secondary malignancies following CAR T-cell therapy was 3.6%, with a median onset time of 26.4 months for solid tumors and 9.7 months for hematologic malignancies. One case involved T-cell lymphoma developing three months after CAR T-cell therapy. The projected five-year cumulative incidence is 15.2% for solid tumors and 2.3% for hematologic malignancies.[26] At Stanford University, 25 of 724 patients developed secondary malignancies with a median follow-up of 15 months. The three-year cumulative incidence of secondary tumors was 6.5%.[27] By December 31, 2023, the FDA had received reports of 22 cases of T-cell lymphoma following treatment with CAR T-cell products, three of which involved viral vectors.[28] Due to the small number of cases and the variation in product use, no firm conclusions can be drawn about the strength of an association with any specific CAR T-cell product.

CONCLUSION

1. Patients with DLBCL who relapse more than one year after initial therapy and achieve chemosensitivity (complete or partial remission) should be considered for autologous stem-cell transplantation.

2. Patients with refractory or relapsed DLBCL within one year of completing initial therapy should be considered for second-line CAR T-cell therapy. Given the potential for cure in 35-40% of these patients, CAR T-cell therapy should be prioritized in the R/R setting. Among the FDA-approved CAR T-cell products, Axi-cel is preferred for fit patients aged 65 years or younger with aggressive disease, while Liso-cel is recommended for older or less fit patients due to its significantly lower risk of neurotoxicity.

3. CAR T-cell therapy should also be considered as a second-line treatment for selected patients with DLBCL who are not candidates for auto-HSCT.

4. Despite the promising outcomes observed in these prospective studies and comparable findings with commercial products, CAR T-cell therapy is underutilized likely because of access, rapidly progressing disease that is not amenable to delay while awaiting manufacturing, and resource utilization. Therefore, CAR T-cell therapy faces significant challenges in low- and middle-income countries due to its high cost and the need for specialized treatment.

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