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RESEARCH ARTICLE

From Stem Cell Transplantation to CAR-T Therapy in Relapse-Refractory Diffuse Large B-Cell Lymphoma

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ABSTRACT
Diffuse large B-cell lymphoma is a highly curable disease when complete remission after immunochemotherapy is achieved. Despite a high complete remission rate, which is a prerequisite for a cure, 20–40% of patients will relapse or fail first-line therapy. Salvage chemotherapy followed by intensification with autologous stem cell transplant (ASCT) has been established as a curative treatment for relapsed chemosensitive patients under 60 years of age. The results have been somewhat disappointing, with less than 50% of patients being eligible for transplant and relapse posttransplant ranging from 60–40%. Improvements have been made with new drugs in development, immunoconjugate bispecific monoclonal antibodies, and chimeric antigen receptor technology (CAR-T). A more precise evaluation of prognostic factors with PET scans and other biological factors during treatment will allow for the design of new treatment strategies. The exceptional response rate in phase 2 achieved with the three available CARTs has now been confirmed with a longer follow-up period. At 2 years, the overall survival (OS) expectancy is 50% with a plateau on the curves. Three randomized studies compared CARTs to the standard of care with ASCT and demonstrated the superiority of CARTs. Despite this superiority, the relapse rate remains 50%, which is significantly better than the standard of care. However, major improvements in OS have not yet been achieved. A clearer definition of eligible patients should also take into account their interim pet-scan, metabolic tumour volume, relation with Ct DNA with follow-up of minimal residual disease.

Keywords: Lymphoma; diffuse large cell; stem cell transplantation; PET scan; relapse; CAR-T; immunochemotherapy

Introduction

Diffuse large B-cell lymphoma (DLBCL) accounts for 40% of newly diagnosed non-Hodgkin's lymphoma cases. It is a heterogeneous entity defined by phenotype and, more recently, by gene profiling expression or molecular genetic profile. It is a highly curable disease. Nevertheless, up to 40% of DLBCL patients will die from their disease despite immunochemotherapy with rituximab, cyclophosphamide, doxorubicin, and vincristine prednisone (RCHOP) [1].

Despite a high complete remission rate, which is a prerequisite for a cure, 20–40% of patients will relapse or fail first-line therapy. Salvage chemotherapy followed by intensification with autologous stem cell transplant (ASCT) has been established as the most unique curative treatment for relapsed chemosensitive patients under 60 years of age [2].

Unfortunately, only half of all patients will be eligible for ASCT regardless of the type of salvage chemotherapy used. Moreover, only 40% of transplanted patients will experience long-term disease-free survival [3,4].

In recent years, several improvements have been made with new drugs, CAR-T-cell technology and a more precise evaluation of prognostic factors with PET scans and other biological factors during treatment.

These improvements have raised questions as to how these tools can be used to reduce the failure rate in young patients with (DLBCL) and propose alternative treatments according to their risk factors in relapsed, refractory patients, with a focus on stem cell transplantation or CAR-T cells.

Several questions are raised in relation to the evaluation of the benefit risk ratio of treatment: When should we define a failure of treatment and shift to salvage—after the end of treatment (EOT) or after 2 or 4 cycles according to an intermediate PET scan? Stem cell transplantation is often considered the last issue after failure of chemoimmunotherapy. Can CAR-T-cell technology replace ASCT in patients with first or later relapses? It will take time and numerous studies to answer all these questions. At the same time, competition with new drugs and bispecific antibodies will challenge CAR-T results.

DLBCL is heterogeneous associated with the development of molecular biology. There is a need to characterize the different subgroups of this cancer. The easiest stratification can be made based on the clinical score of the international prognostic index (IPI) considering age, stage, LDH, performance status, and number of extranodal involvement. The choice of using these parameters was based upon the largest multivariate analysis in DLBCL [5]. It was robust and validated in the rituximab era and defines four different subgroups with 5-year relapse rates of 32%, 46%, 69% and 83%, making comparison of the population easier. This score can be improved by more clearly defining some parameters (NCCN-IPI) [6,7]. These parameters remain the basis for comparison to new biological parameters.

In addition, two main DLBCL subgroups have been defined with cells of origin, germinal centre B cells, GCB or non-GCB, by immunophenotype or gene profiling with a slightly better prognosis for the GCB subtype depending on the series and treatment used [8,9]. More recently, with NGS, five relevant genetic subtype groups have been proposed reflecting variation within subgroups of DLBCL and were integrated into the development of LymphGen classification [10].

Other gene rearrangements have been described. The focus has been on C MYC and BCL2, which are associated with poor prognosis and define high-grade lymphoma (HGL) [11]. However, they represent less than 15% of the population.

Current chemotherapy strategies have tried to consider the heterogenous characteristics of this disease. New agents that target molecular signalling are in development. Combinations including R-CHOP and targeted agents have been tested in randomized studies. At the present time, none of these combinations have demonstrated an important significant effect on survival [12, 13, 1].

Standard of care for relapses: When should we change our practice?

Waiting for relapse or early progression has strong limitations. Only half of all patients are eligible for transplantation, and half will relapse later on. The COllaborative trial in Relapsed Aggressive Lymphoma (CORAL) study was designed as an international effort to determine which salvage regimens should be proposed for patients with relapsed DLBCL and to evaluate the place of rituximab for maintenance after ASCT [3]. Some of the conclusions of this study were disappointing. With the secondary international prognostic tindex (sIPI), a relapse/refractory episode <12 months from diagnosis and prior rituximab exposure were significantly associated with poor response to salvage and survival in multivariate analyses. Only half of patients are chemosensitive and eligible for transplantation, and half will relapse later with 5-year progression-free survival (PFS) and OS rates of 23% and 34%, respectively, based on the CORAL study. The 3-year PFS for the 242 patients who underwent "per protocol" transplantation was

52% [3].There were no difference between CR and PR patients after salvage if submitted to transplantation, with a 3-year PFS of 53%.
At 5 years, at the end of the curves, a similar plateau was observed. However, the Cox model revealed that sIPIs 2 and 3 remained significant adverse factors (P <.0004; hazard ratio, 2.252). The main limitation of these transplantation strategies is the need for a significant level of response to the salvage regimen to reach complete remission or a good partial response before ASCT. Notably, 45% of patients had to receive more than 2 lines of therapy to reach a chemosensitive status. However, a fairly good prognosis was observed for patients transplanted with IPI 0-1, with a 4-year PFS of 63% and an OS of 72%. The results of this study, which had a longer follow-up, challenge those obtained after CAR-T application. These results require careful evaluation of the different treatment strategies in first relapse utilized in these patients.
Salvage chemotherapy followed by autologous stem cell transplantation remains a standard second-line treatment for relapsed and refractory diffuse large B-cell lymphoma (DLBCL) without adverse prognostic factors. sIPI 0-1.

However, the strategy is not adequate in patients who require third-line treatment. Updated outcomes of 203 patients who could not proceed to scheduled ASCT in the CORAL study [14] were reviewed. In the intent-to-treat analysis, the overall response rate to third-line chemotherapy was 39%, with 27% CR or CR unconfirmed and 12% PR. The median OS of the entire population was 4.4 months. Among the 203 patients, 64 (31.5%) were eventually transplanted (ASCT 56 pts, allogeneic SCT 8 pts). OS was significantly improved in patients who underwent transplantation, with a 1-year OS of 41.6% compared with 16.3% for those who did not receive transplantation (P< 0.0001). In multivariate analysis, transplantation (HR 0.375) independently predicted OS. Third-line salvage chemotherapy can achieve a poor response rate, allowing long-term survival in a few DLBCL patients when followed by transplantation. However, improvement of salvage efficacy is an urgent need with new drugs.
The SCHOLAR-1 international retrospective study included patients from two randomized studies and two academic registries and highlighted the poor clinical outcomes and survival among patients with refractory large B-cell lymphoma treated with conventional chemotherapy [15].
Among 861 DLBCL patients, 636 were included after meeting the refractory disease inclusion criteria. Refractory DLBCL was defined as progressive disease (received >4 cycles of first-line therapy) or stable disease (received 2 cycles of later-line therapy) if they had a good response to chemotherapy or relapse <12 months after ASCT.
For patients with refractory DLBCL, the objective response rate was 26% (complete response rate, 7%) to the next line of therapy, and the median OS was 6.3 months.
Response to therapy was significantly associated with longer survival, particularly for patients who submitted to ASCT thereafter. These results showed that 20% of patients remained alive at 2 years; however, these long-term durable responses were primarily driven by the minority of patients who received ASCT and/or achieved a CR or PR. Thirty-one patients who achieved CR underwent ASCT, and their median OS was more than 6 years at the time of this analysis. Fifty-seven patients who received ASCT were alive at the last follow-up (range, 1-14 years) and represent the tail of the Kaplan–Meier curve of OS. Most patients (73%) did not respond to salvage therapy or were not able to receive ASCT, resulting in particularly poor outcomes.

Allo transplant or CAR-T: Is there room for a possible salvage?
Allogeneic SCT has been shown to achieve long-term disease-free survival in patients who have failed a previous ASCT [16]. A total of 101 patients (57 males; median age, 46 years) from the European blood marrow transplantation (EBMT) registry were analysed. A myeloablative conditioning regimen was used in 37 patients, and reduced intensity conditioning (RIC) was used in 64 patients. The three-year NRM (not related mortality) was 28.2%, RR was 30.1%, PFS was 41.7% and OS was 53.8%.
In contrast to ASCT, high-dose therapy and allogeneic stem cell transplant (alloSCT) have rarely been employed in DLBCL in first-line salvage largely as a result of the significant toxicity reported in early studies of this modality. In registry data coming from EBMT [17], the outcome of standard salvage therapy with an autologous stem cell transplant (ASCT) over the last two decades and the outcome of (alloSCT) in the most recent decade were compared. Two hundred thirty patients received an alloSCT (myeloablative (MACalloSCT) n = 132, reduced intensity (RICalloSCT) n = 98). The 4-year NRM rates were 7%, 20% and 27% for ASCT, RICalloSCT and MACalloSCT, respectively. The 4-year PFS rates were 48%, 52% and 35% for ASCT, RICalloSCT and MACalloSCT, respectively. The 4-year OS was

60%, 52% and 38% for ASCT, RIC alloSCT and MACalloSCT, respectively. After adjustment for confounding factors, NRM was significantly worse for patients undergoing alloSCT, while there was no difference in the relapse incidence.

In a noncomparative registry analysis with CAR-T from the CIBMTR (Center for International Blood & Marrow Transplant Research), a total of 584 patients were included and the outcomes of patients with DLBCL (>18 years) undergoing reduced intensity alloHCT (403 pts) or CAR-T (181 pts) therapy with axicabtagene ciloleucel from 2012 to 2019 after a prior auto-HCT failure were reported [18]. The 1-year OS of alloHCT recipients was classified into low-, intermediate- and high/very high-risk groups according to the CIBMTR prognostic score, which was 73.3%, 59.9%, and 46.3%, respectively (P =.002). The corresponding rates for low-, intermediate-, and high/very high-risk CAR-T patients were 88.4%, 76.4%, and 52.8%, respectively (P < 0.001).

Allogeneic transplantation may be another method for reducing posttransplantation relapse; it has shown promising results and resulted in disease control at 3 years of 35% in people who had poor prognosis relapses. Although this method does solve the issue of salvage efficacy before transplantation, it is restricted to patients younger than those in this report, in whom more than 50% of the patients were >60 years old. This very large series clarifies some of the main issues concerning the efficacy of transplantation in the rituximab era. Even for poor prognosis relapses, if patients can achieve CR or partial response before transplantation, long-term survival can be expected for 50% of the patients, with a 3-year PFS of 44%. Even though progress still must be made, ASCT remains the standard of care for patients with relapsed DLBCL.

Significant improvement in third- or second-line treatment with CAR-T cells:

CAR-T-cell therapy was developed from fusion proteins containing an extracellular antigen-binding domain initiating T-cell signalling and T-cell effector functions with antitumour efficacy. The modified T cells of the patient are expanded and reinfused. Axicabtagene ciloleucel (axi-cel), an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, was first approved in multiple countries for the treatment of patients with relapsed or refractory large B-cell lymphoma after failure of 2 or more systemic therapies [19].

Three main CAR-T constructs have now been registered based on three single-arm pivotal studies for the treatment of relapse-refractory DLBCL after 2 lines of chemotherapy. All of these studies provided similar clinical results, with some differences among the studies in terms of their inclusion criteria and bridging therapy before transplant [20].

Clinical trials have demonstrated that CAR-T-cell treatments induce long-term remission in approximately 40–50% of patients at 5 years.

The first trial, Axicaptagene ciloleucel, was evaluated in the ZUMA 1 trial [19]. No intensive bridging therapy was allowed. Of 101 patients, 83% treated with axicabtagene ciloleucel for refractory DLBCL achieved an objective response, and 58% of patients achieved CR, with a median follow-up of 63 months. The five-year OS was 42%, with a median of 23 months.

Tisagenlecleucel was evaluated in the JULIET trial [20]. Of the 115 infused patients, bridging therapy allowed an ORR of 54%, with a 40% CR rate and 13% PR rate. The ORR was consistent across prognostic subgroups, including those with prior autologous SCT and double/triple-hit lymphoma. The probability of being relapse-free was 66% at 6 months and 64% at 12 and 18 months. The OS probability was 48% at 12 months and 43% at 18 months.

In the TRANSCEND trial [21], lisocabtagene maraleucel was evaluated in 270 heavily pretreated patients with aggressive diseases. Bridging therapy was used in 159 patients. The ORR was 73%, with a CR rate of 53%; responses were similar across patient subgroups. With 23 months of follow-up, the median DoR, PFS, and OS were 23.3 months, 6.8 months, and 27.3 months, respectively.

Real-world data confirm the initial results of these studies [22,23]. In reports from 17 institutions, of 298 R/R DLBCL patients who underwent leukapheresis, 275 (92%) received axi-cel therapy [22]. The best overall and complete response rates in infused patients were 82% and 64%, respectively. At a median follow-up of 12.9 months, median progression-free survival was 8.3 months and median overall survival was not reached. In another US study [23]. One hundred twenty-two patients from 7 medical centres were treated with axi-cel. The best overall and complete response (CR) rates were 70% and 50%, respectively. Median DOR and progression-free survival (PFS) were 11.0 and 4.5 months.

Data for all three CARTs were registered with a historical comparison of patients who were refractory to first salvage therapy. The choice of comparator for registration was the CORAL study

[3] or the SCHOLAR 1 [15] study, which incorporated the data from CORAL.

Patients included in SCHOLAR-1 were compared with the 2-year outcomes of ZUMA-1 [24]. Prior to this comparison of clinical outcomes, propensity scoring (based on a broad set of prognostic covariates) was used to create a balance between ZUMA-1 (101 patients) and SCHOLAR-1 (424 patients). The objective response rate and complete response rate were 83% and 54% in ZUMA-1 vs. 34% and 12% in SCHOLAR-1, respectively. The 2-year survival rate was 54% in ZUMA-1 and 20% in SCHOLAR-1, and a 73% reduction in the risk of death was observed in ZUMA-1 vs. SCHOLAR-1. Despite the limitations of this nonrandomized analysis, these results indicate that axi-cel produces durable responses and a substantial survival benefit vs. non–CAR-T-cell salvage regimens for patients with refractory DLBCL. It is also crucial to assess whether this disease allows for curative treatment with CAR-T.

An indirect comparison of the OS and overall response rate (ORR) associated with tisagenlecleucel was made using data from the JULIET vs. historical treatments assessed in the CORAL study. Propensity score weighting using standardized mortality ratio weight and fine stratification weight was used to compare OS and ORR, adjusting for baseline confounders [25]. The median OS was 12.48 months (JULIET) vs. 4.34 to 4.40 months (CORAL) for the FAS population and 8.25 (JULIET) months vs. 4.04 to 4.86 (CORAL) months for the ITT population. Tisagenlecleucel was associated with a significantly higher ORR of 55% compared with 31% for the historical control.

Neurotoxicities, ICANS, cytokine release syndrome, CRS, and grade 4 were manageable even in elderly patients > 65 years. This finding opened the door to salvage with CARTs for patients not eligible for transplantation.

The three CAR-Ts have significant specific toxicities, leading to strict guidelines. In the absence of randomized comparison between the registered products, it is difficult to truly know if there were significant differences in the incidence of grade 3-4 toxicities. It seems, however, that axi-cel has slightly more severe neurotoxicity.

Evolving treatment in second-line randomized studies?

Standard of care SoC studies have shown that patients with multiple lines of treatment, bulky disease, high LDH or metabolic tumour volume (MTV) still have a poor prognosis. In predicting curability in patients with relapsed/refractory R/R DLBCL, individual patient-, disease-, and treatment-related factors must be considered. Approximately 50% of patients are eligible for transplantation. Only 50% will respond to salvage treatment and be candidates for stem cell transplantation. However, 50% will relapse depending on prognostic factors. Only 25% of transplanted patients are expected to be cured. A small fraction can be salvaged by allotransplant in case of relapse. However, it is unclear whether we should replace ASCT with CAR-T in late relapse?

The results of three randomized studies comparing standard of care (SOC) in first relapsed refractory DLBCL with salvage chemotherapy followed whenever possible with ASCT and a high-dose treatment conditioning regimen have been reported. **Table 1**

The patients included in the first study, which examined axi-cel, have matured enough for a comprehensive report. Since CAR-T-cell therapy may benefit patients in earlier lines of therapy, ZUMA-7 was a global, randomized, phase 3 trial of axi-cel vs. SOC in patients with two lines of R/R LBC [26]. Eligible patients were ≥18 y with DLBCL, ECOG PS 0–1, R/R disease ≤12 months of adequate first-line chemoimmunotherapy, and intention to proceed to HDT-ASCT. Patients were randomized 1:1 to axi-cel or SOC. Patients received a single infusion of 2×10^6 CAR-T cells/kg after conditioning. The median delay between leukapheresis and infusion was 13 days. Optional bridging therapy was limited to glucocorticoids. In the SOC arm, patients received 2–3 cycles of an investigator-selected, protocol-defined, platinum-based chemoimmunotherapy (CIT) regimen; patients with partial response or complete response proceeded to HDT-ASCT. Of 180 patients randomized to axi-cel, 170 (94%) were infused; of the 179 patients randomized to SOC, 64 (36%) reached HDT-ASCT after 2 lines of CIT. At the 24.9-month median follow-up, the median EFS was significantly longer with axi-cel vs. SOC 8.3 months vs. 2 months, respectively (HR: 0.398; $P<.0001$), and Kaplan–Meier estimates of the 24-month EFS rates were significantly higher with axi-cel (41% vs. 16%). Among randomized patients, ORR and CR rates were higher with axi-cel vs. SOC (ORR: 83% vs. 50%, $P<.0001$]; (CR: 65% vs. 32%). Safety of axi-cel was manageable. Axi-cel may thus replace CIT/HDT-ASCT as the SOC for second-Line R/R LBCL. In this study, even the subgroup of 51 patients over 65 years experienced a persistent advantage for CAR-T with a 2-year EFS at 47% vs. 15% for SOC.

The phase 3 Transform [27] randomized trial was a similar study with liso-cel, a CD19- CAR-T-Cell

Therapy, Versus Standard of Care with Salvage Chemotherapy followed by Autologous Stem Cell Transplantation as second-Line (2 L) treatment in Patients with Relapsed or Refractory Large B-Cell Lymphoma. Patients in Arm A received 3 cycles of CIT. The responding patients (CR or PR) were to proceed to BEAM + ASCT. Patients in arm B underwent lymphodepletion with fludarabine/cyclophosphamide followed by liso-cel at a target dose of 100 × 10^6 CAR^+ T cells. The main difference from the previous study was that bridging therapy with an Arm A CIT regimen was allowed. Crossover to receive liso-cel was allowed in Arm A. A total of 184 patients were randomized, with 92 patients in each arm. For arms A and B, the median EFS was 2.3 vs. 10.1 months (HR, 0.349; $P < 0.0001$), the median PFS was 5.7 vs. 14.8 mo (HR, 0.406; $P = 0.0001$), and the CR rate was 39% vs. 66% ($P < 0.0001$). No new safety concerns were identified for liso-cel, a potential new SOC for 2 L treatment in patients with R/R LBCL.

Table 1: Three randomized studies comparing standard of care (SOC) in first relapsed refractory DLBCL with salvage chemotherapy followed whenever possible with ASCT and a high-dose treatment conditioning regimen

	ZUMA-7		BELINDA		TRANSFORM	
TRIAL	**Axi-Cel N = 180**	**SOC N = 179**	**Tisa-Cell N = 162**	**SOC N = 160**	**Liso-Cell N = 92**	**SOC N = 92**
Study Design						
Inclusion criteria	Refractory or relapsed within 12 months of 1st line		Refractory or relapsed within 12 months of 1st line		Refractory or relapsed within 12 months of 1st line	
Primary Endpoint[b]	EFS		EFS after week 12		EFS	
Crossover[c]	Off study		Allowed		Allowed	
Treatments						
CAR-T Arm						
CAR-T Product	Axi-cel		Tisa-Cel		Liso-cel	
CAR-T-cell dose	2 x 10^6/kg		0.6–6 x 10^8 Median 2.9 x 10^8		1 x 10^6/kg	
Lymphodepletion	Flu 30 mg/m² Cy 500 mg/m² X 3 days		Flu 30 mg/m² Cy 300 mg/m² X 3 days		Flu 25 mg/m² Cy 250 mg/m² X 3 days	
Bridging	Steroids only		Allowed		Allowed	
Control Arm						
Salvage	2nd line CIT		2nd line CIT 3rd line allowed		2nd line CIT	
Median age	58 (21-80)	60 (26-81)	59.5 (19-79)	58 (19-77)	60 (54-68)	58 (42-65)
Male – no. (%)	110 (61)	127 (71)	103 (64)	98 (61)	44 (48)	61 66)
ECOG PS 1- no. (%)	85 (87)	79 (44)	70 (43)	65 (41)	44 (48)	35 (38)
Disease stage – no. (%)						
I or II	41 (23)	33 (18)	55 (34)	62 (39)	NR	NR
III or IV	139 (77)	146 (82)	107 (66)	98 (61)	NR	NR
Second-line aaIPI 2-3 -no. (%)	82 (46)	79 (44)	NR	NR	36 (39)	37 (40)
Second-line IPI > 2 – no. (%)	NR	NR	106 (65)	92 (58)	NR	NR
Disease type – no. (%)						
DLBCL	126 (70)	120 (67)	101 (62)	112 (70)	53 (58)	49 (53)
High grade BCL including rearrangement of MYC with BCL2 or BCL6 or both	31 (17)	25 (14)	32 (20)	19 (12)	22 (24)	21 (23)
Not confirmed or missing data	18(10)	28 (46)	-	-	-	-
Other	5 (3)	5 (3)	22 (14)	21 (13)	17 (18)	22 (24)
Molecular subgroup -no. (%)						
GCB	109 (61)	99 (55)	46 (28)	63 (39)	NR	NR
ABC	16 (9)	9 (5)	52 (32)	42 (26)	NR	NR
Missing data	28 (16)	41 (23)	NR	NR	NR	NR
Response to 1st line therapy – no. (%)						
Primary refractory	133 (74)	131 (73)	107 (66)	107 (67)	67 (73)	68 (74)
Relapse ≤ 12 months	47 (26)	48 (27)	-	-	25 (27)	24 (26)
Relapse < 6 months	NR	NR	30 (19)	32 (20)	NR	NR
Relapse 6-12 months	NR	NR	25 (15)	21 (13)	NR	NR
Primary end point EFS Months	8,3 m	2,0 m	3 m	3 m	10,1 m	2,3 m

Locke et al., NEJM 2022, Bishop et al., NEJM 2022, Kamdar et al., Lancet 2022

In both studies, the follow-up was still too short, but a trend in improved OS was already apparent.
In the last study, BELINDA [28], 322 patients were randomly assigned to receive tisagenlecleucel with optional bridging therapy (tisagenlecleucel group) or salvage chemotherapy and autologous haematopoietic stem cell transplantation. The median delay between leukapheresis and infusion was 52 days. A response occurred in 46.3% of the patients in the tisagenlecleucel group and in 42.5%

in the standard of care group. The median event-free survival in both groups was 3.0 months. Tisagenlecleucel was not superior to standard salvage therapy in this trial. Bridging therapy is frequently used to stabilize rapidly proliferative disease and was allowed in this trial owing to the enrolment of patients with high-risk aggressive lymphoma and the expected delayed time to infusion.

In the first two studies, an impressive complete response rate, with a negative PET scan, was related to CAR-T-cell infusion of 65% and 66%. The quality of response after the infusion of CAR-T treatment is associated with a better outcome, a goal never achieved with any salvage chemoimmunotherapy regimen. However, the relapse rate remains an issue, and the next generation of CARTs or approaches will have to focus on this aspect. The quality of response after CAR-T treatment also demonstrates, along with registry data, that bridging therapy, if necessary, with intensive standard treatment is not associated with an improvement of response. The role of T-cell depletion before apheresis is likely to affect CAR-T-cell efficacy. New salvage with less T-cell-depleting treatments should be incorporated with new drugs. Patients clearly progressing with positive PET scans should be excluded from receiving this treatment.

Relapsed DLBCL patients in partial remission (PR) after salvage?

Clinicians should discuss patients' eligibility for standard ASCT, potentially including patients without adverse factors following a negative PET scan[29].

In the CORAL study, for patients who underwent ASCT, the 3-year PFS was 53%. There was no difference between the patients who achieved radiologic CR or PR just before ASCT [30]. The relative efficacy of autologous haematopoietic cell transplantation versus chimeric antigen receptor T-cell CAR-T therapy in diffuse large B-cell lymphoma patients who achieve PR after salvage chemotherapy is not known. Using the Center for International Blood & Marrow Transplant Research registry database [31], Shadman et al. identified 266 adult DLBCL patients who received auto-SCT and 145 CAR-T treatment with axicabtagene ciloleucel. Patients had to achieve only a PR after salvage while in a PR by CT or PET scan. Pretransplant or pre-CAR-T imaging with either PET or computed tomography scans was acceptable, but patients with an available negative PET scan (Deauville 1-3) were excluded from the study. The clinical outcomes were compared between the two cohorts using univariable and multivariable regression models after adjustment for relevant baseline and clinical factors with propensity scores. The 2-year progression-free survival (52% vs. 42%; p=0.1) and the rate of 100-day nonrelapse mortality (4% vs. 2%; p=0.3) were not different between the 2 cohorts, but consolidation with auto-SCT was associated with a lower rate of relapse/progression (40% vs. 53%; p=0.05) and superior OS (69% vs. 47%; p=0.004) at 2 years. These data, in agreement with the CORAL study, support the role of auto-SCT as the standard of care in transplant-eligible patients with relapsed DLBCL in PR after first salvage therapy.

These data suggest the need for a randomized study on relapsed patients still in PR after chemoimmunotherapy followed by ASCT compared to patients submitted to CAR-T. This study would standardize the definition of PR patients after a defined number of cycles of CIT. Registry data now have a long follow-up, and the percentage of cured patients after ASCT is evaluable at 10 years, while data for CAR-T are still immature.

Response adapted trials design: Place of pet-scan before CART, interim PET

High-risk patients are not accurately identified by the current prognostic scoring systems, such as the International Prognostic Index. There are new tools allowing a better predictive value of the outcome. Over the last 5 years, the prognostic role of quantitative PET parameters was underlined, in particular that tumour metabolic volume (MTV) could have at diagnosis and at relapse a major prognostic value independent of another factor [32]. MTV reflects the total volume of 18F-FDG–avid tumour regions within the whole body and hence provides a more comprehensive tumour burden evaluation than previous surrogates, such as lactate dehydrogenase levels.

Patients receiving CAR-T with a high tumour burden are at higher risk for treatment failure and shorter survival than those with a low tumour burden. The independent factors predicting relapse and early relapse were the number of extranodal EN sites >2, high CRP, and TMTV >.80 mL; the highest hazard ratio was for the number of extranodal sites >2 and TMTV [33].

This new adverse parameter remains valid for relapsed patients receiving CAR-T therapy. Nevertheless, metrics need to be standardized before extending this marker in clinical practice [34]. Baseline high-risk factors, including LDH and ECOG PS [35,33], inform patient selection pre-CAR-T, but by the time patients have undergone treatment and responded, an individual patient's risk will have changed. On-treatment biomarkers, including imaging markers of response e.g., Deauville score

(DS) or disease metabolic volume kinetics [36], should be incorporated into a dynamic, postinfusion risk model. FDG-PET scan imaging using the 5-point DS is the gold-standard assessment for end-of-treatment response in DLBCL [37]. The interim PET response provides prognostic information in R-CHOP-treated patients [38], and PET-driven treatment strategies have been investigated [39].

In a retrospective report, 130 patients were stratified by the 1-month post-CAR-T DS. DS 1 or 2 patients had a 15% risk of failure and were spared additional treatment with potential toxicity. DS 3 to 4 patients with a 30% to 45% risk of early CAR-T-cell failure benefited from combinatorial approaches [35]. Response-adapted trial designs of CAR-T cells in combination with immunomodulatory agents are an attractive concept.

In conclusion, these results indicate that early FDG-PET DS categories provide a standardized, broadly available tool to predict durable remission after CD19 CAR-T and inform early post–CAR-T management and response-adapted stratification in clinical trials.

Future directions: circulating tumour DNA to Evaluate residual disease and mutational genotyping

In the case of several haematological diseases, the quality of response to treatment is correlated with a negative minimal residual disease. Until recently, this approach was difficult in DLBCL due to the absence of easily detectable minimal disease by PCR or immunochemistry. With the recognition of circulating tumour cell CtDNA, it is now possible to follow the quality of response during evolution [40]. The additional prognostic value of circulating tumour DNA (CtDNA) before and during therapy can predict patient outcomes. In the study from Kurtz [40], the dynamics of CtDNA from 217 patients treated at six centres using a training and validation framework were evaluated. Before therapy, ctDNA was detectable in 98% of patients; pretreatment levels correlated with MTV and were prognostic in both front-line and salvage settings. In the discovery set, ctDNA levels changed rapidly, with a 2-log decrease after one cycle (early molecular response [EMR]) and a 2.5-log decrease after two cycles (major molecular response [MMR]) stratifying outcomes. In the first validation set, patients receiving front-line therapy achieving EMR or MMR had superior outcomes at 24 months (EMR: EFS, 83% v 50%; P =.0015; MMR: EFS, 82% v 46%; P.001). The prognostic value of EMR and MMR was further confirmed in multivariable analyses, including prognostic index and interim positron emission tomography/computed tomography scans, across both cohorts. Molecular response was an independent prognostic factor for outcomes, including event-free and overall survival. Circulating tumour DNA is not a single assay but can reveal multiple dimensions of a tumour. Dissecting liquid biopsies of aggressive B-cell lymphoma patients revealed novel quantitative, mutational, and fragmentation patterns in ctDNA that can resolve undisclosed heterogeneity and identify patients with incomplete responses and inferior outcomes following uniform therapy [41]. ctDNA is used to detect MRD and/or genotype tumours. ctDNA and other risk markers can be combined into dynamic risk profiling for optimal patient stratification. This finding anticipates a pivotal role for pretreatment ctDNA analysis in future clinical trial designs and treatment decisions.

Conclusion

Until recently, SOC for relapsed/ refractory DLBCL was curative salvage CIT restricted to young patients responding to immunochemotherapy followed by ASCT. However. only half of the patients are eligible for transplantation. Moreover, patients over 65 years were generally excluded from this procedure due to comorbidities. The rapid development of CAR-T cells offers now an opportunity in several situations, to salvage patients non eligible to transplant with CAR-T cells and changes the paradigm of treatment, including more elderly patients with a manageable control of immune-cell toxicities. Half of the relapsed/refractory patients are expected to be free of disease after 2 years and longer. It is better than SOC but a high cure rate is not reached. The rate of relapses post infusion CAR-T cells can be high in patients with positive PET scans and high MTV. The use of bridging therapy with conventional immunochemotherapy was not followed by success in randomized study. The potency of CAR-T cells was not enhanced when generated from patients later in their treatment course. Patients with a partial response after CIT can be candidates for CAR-T but are challenged by the coexistence of standard salvage with ASCT depending on their prognostic factors [42]. The evaluation of new approaches with bispecific monoclonal antibodies or new constructs CARTs are promising but randomized studies with long follow-ups are necessary.

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