LYMPHOID NEOPLASIA

Autologous transplant vs chimeric antigen receptor T-cell therapy for relapsed DLBCL in partial remission

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KEY POINTS

- In patients with DLBCL in PR postsalvage, auto-HCT and CAR-T gave 2-year progression-free survival (PFS) of 52% vs 42% and OS of 69% vs 47%.

- In patients with ≤2 prior lines of therapy, there was no difference in PFS or OS between the 2 groups.

The relative efficacy of autologous hematopoietic cell transplant (auto-HCT) vs chimeric antigen receptor T-cell (CAR-T) therapy in patients with diffuse large B-cell lymphoma (DLBCL) who achieve a partial remission (PR) after salvage chemotherapy is not known. Using the Center for International Blood & Marrow Transplant Research registry database, we identified adult patients with DLBCL who received either an auto-HCT (2013-2019) or CAR-T treatment with axicabtagene ciloleucel (2018-2019) while in a PR by computed tomography or positron emission tomography scan. We compared the clinical outcomes between the 2 cohorts using univariable and multivariable regression models after adjustment for relevant baseline and clinical factors. In the univariable analysis, the 2-year progression-free survival (52% vs 42%; P = .1) and the rate of 100-day nonrelapse mortality (4% vs 2%; P = .3) were not different between the 2 cohorts, but consolidation with auto-HCT was associated with a lower rate of relapse/progression (40% vs 53%; P = .05) and a superior overall survival (OS) (69% vs 47%; P = .004) at 2 years. In the multivariable regression analysis, treatment with auto-HCT was associated with a significantly lower risk of relapse/progression rate (hazard ratio = 1.49; P = .01) and a superior OS (hazard ratio = 1.63; P = .008). In patients with DLBCL in a PR after salvage therapy, treatment with auto-HCT was associated with a lower incidence of relapse and a superior OS compared with CAR-T. These data support the role of auto-HCT as the standard of care in transplant-eligible patients with relapsed DLBCL in PR after salvage therapy.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is a curable disease, and ~60% of patients do not require further treatment after an initial anthracycline-based and rituximab-containing regimen. However, outcomes of patients who are not cured with first-line treatment are poor, and defining the optimal treatment strategy remains to be an unmet clinical need.[1] The current standard of care for fit patients with relapsed/refractory DLBCL, including for patients with early therapy failure (defined as relapse or progression in ≤1 year from original diagnosis), comprises treatment with an alternative salvage regimen(s) followed by high-dose chemotherapy and autologous hematopoietic cell transplant (auto-HCT) consolidation in those who achieve either complete remission (CR) or partial remission (PR).[2-4] Although there seems to be a universal agreement in this approach for patients who achieve a CR, the practice is less uniform in the case of PR patients because they are also potential candidates for chimeric antigen receptor T-cell (CAR-T) therapy.[5-7]

Table 1. Baseline characteristics of DLBCL patients who received auto-HCT or CAR-T while in a PR

	Auto-HCT	CAR-T	P value*
Number of patients†	266	145	
Number of centers	88	40	
Demographics			
Patient age			
Median, y (range)	58 (18-80)	60 (24-91)	.07‡
≥60 y (%)	118 (44)	73 (50)	.25§
Male sex	167 (63)	89 (61)	.78§
Race			<.001§
Caucasian	166 (62)	123 (83)	
African American	58 (22)	10 (7)	
Other‖	11 (4)	1 (1)	
Missing	11 (4)	7 (5)	
At diagnosis			
Stage at diagnosis			.99§
III-IV, no. (%)	163 (61)	80 (55)	
Missing	42 (16)	35 (24)	
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements, no. (%)	10 (16)	25 (17)	.84§
Missing (not collected before 2018)	204		
LDH elevated at diagnosis	74 (28)	37 (26)	.53§
Missing	152 (57)	92 (63)	
Extranodal involvement at diagnosis, no. (%)	136 (51)	72 (50)	.51§
Missing	42 (16)	19 (13)	
Prior treatments			
Refractory to first-line therapy, no. (%)	160 (60)	79 (55)	.61§
Missing	6 (2)	22 (15)	
Time from diagnosis to auto-HCT or CAR-T, mo, no. (%)			.30§
≤12 mo	103 (39)	64 (44)	
>12 mo	162 (61)	81 (56)	
Missing	1 (0)	0	
Lines of therapy before auto-HCT or CAR-T			
Median (range)	2 (1-6)	3 (2-11)	<.001‡
More than 2 lines, no. %	89 (33)	97 (67)	<.001§0
Number of prior treatment lines			
1	48 (18)	0	
2	124 (47)	42 (29)	
3	55 (21)	52 (36)	
4	22 (8)	23 (16)	
5 or more	12 (4)	22 (15)	
Missing	5 (2)	6 (4)	

BEAM, carmustine, etoposide, cytarabine and melphalan; Bu/Cy, busulfan/cyclophosphamide; CBV, cy, carmustine, etoposide; CT, computed tomography; Flu/Cy, fludarabine, cyclophosphamide; KPS, Karnofsky performance score; LDH, lactate dehydrogenase.

*P values were calculated ignoring the missing values.

†This includes 11 patients with primary mediastinal large B-cell lymphomas in the auto-HCT group and 4 in the CAR-T therapy group.

‡Hypothesis testing Kruskal-Wallis test.

§Hypothesis testing Pearson χ^2 test.

‖Patient race – other: auto-HCT: 1 native Hawaiian or other Pacific islander, 5 American Indian or Alaska Native, 5 more than 1 race. CAR-T: 1 more than 1 race.

Table 1. (continued)

	Auto-HCT	CAR-T	P value*
Pre auto-HCT or CAR-T			
KPS			.09§
≥90	136 (51)	56 (39)	
Missing	2 (3)	13 (9)	
Largest node before auto-HCT or CAR-T, no. (%)			.05§
<3 cm	41 (15)	21 (15)	
3-5 cm	65 (24)	26 (18)	
>5 cm	76 (29)	60 (41)	
Missing	84 (32)	38 (26)	
Imaging before auto-HCT or CAR-T, no. (%)			.36§
PET or PET/CT	222 (83)	126 (87)	
CT	44 (17)	19 (13)	
Conditioning regimen, no. (%)			
BEAM	203 (76)	N/A	
Bu/Cy	15 (6)	N/A	
CBV	43 (16)	N/A	
Other	43 (16)	N/A	
Lymphodepletion regimen, no. (%)			
Flu/Cy	N/A	145 (100)	
Year of auto-HCT or CAR-T, no. (%)			<.001§
2018 and after	66 (20)	145 (100)	
Follow-up, median, mo (range)	38 (3-79)	12 (3-26)	

BEAM, carmustine, etoposide, cytarabine and melphalan; Bu/Cy, busulfan/cyclophosphamide; CBV, cy, carmustine, etoposide; CT, computed tomography; Flu/Cy, fludarabine, cyclophosphamide; KPS, Karnofsky performance score; LDH, lactate dehydrogenase.

*P values were calculated ignoring the missing values.

†This includes 11 patients with primary mediastinal large B-cell lymphomas in the auto-HCT group and 4 in the CAR-T therapy group.

‡Hypothesis testing Kruskal-Wallis test.

§Hypothesis testing Pearson χ^2 test.

‖Patient race – other: auto-HCT: 1 native Hawaiian or other Pacific islander, 5 American Indian or Alaska Native, 5 more than 1 race. CAR-T: 1 more than 1 race.

Recently, the Center for International Blood and Marrow Transplant Research (CIBMTR) reported high clinical efficacy of auto-HCT in patients with DLBCL who received an auto-HCT while in a positron emission tomography (PET)-positive PR, with a 5-year progression-free survival (PFS) rate of ~40%.[8] Efficacy of auto-HCT vs CAR-T cell therapy for patients with DLBCL achieving a PR as the best response to therapy has not been compared in prospective trials. Ongoing randomized trials in the subset of patients with DLBCL with early treatment failure are comparing salvage therapy followed by auto-HCT consolidation in responding patients vs proceeding directly with CAR-T treatment without attempting salvage therapy (NCT03570892, NCT03575351, and NCT03391466). However, these trials are not designed to address the management of patients with DLBCL already achieving a PR in response to salvage therapies. This question is highly clinically relevant because patients with relapsed DLBCL are often referred to transplant or cell therapy programs only after starting salvage therapy.

Using the CIBMTR database, we compared the outcomes of patients with DLBCL who achieved a PR as the best response to therapy and received either auto-HCT or CAR-T treatment.

Methods
Data source
For details of the data source, please refer to the supplemental material available on the *Blood* Web site. This study is approved by the Medical College of Wisconsin and the National Marrow Donor Program institutional review boards.

Patients
Adult patients (age ≥18 years) with DLBCL, high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements or primary mediastinal large B-cell lymphoma who achieved a PR per international working group criteria[9,10] and underwent either an auto-HCT between 2013 and 2019 or CAR-T treatment with axicabtagene ciloleucel (axi-cel) between 2018 and 2019 were included in this analysis. Pretransplant or pre-CAR-T imaging with either PET or computed tomography scans were acceptable, but patients with an available negative PET scan (Deauville 1-3) were excluded from the study because they would not meet the PR criteria per the 2014 Lugano definition.[9] Patients in the CAR-T cohort with a prior auto-HCT were excluded from the analysis.
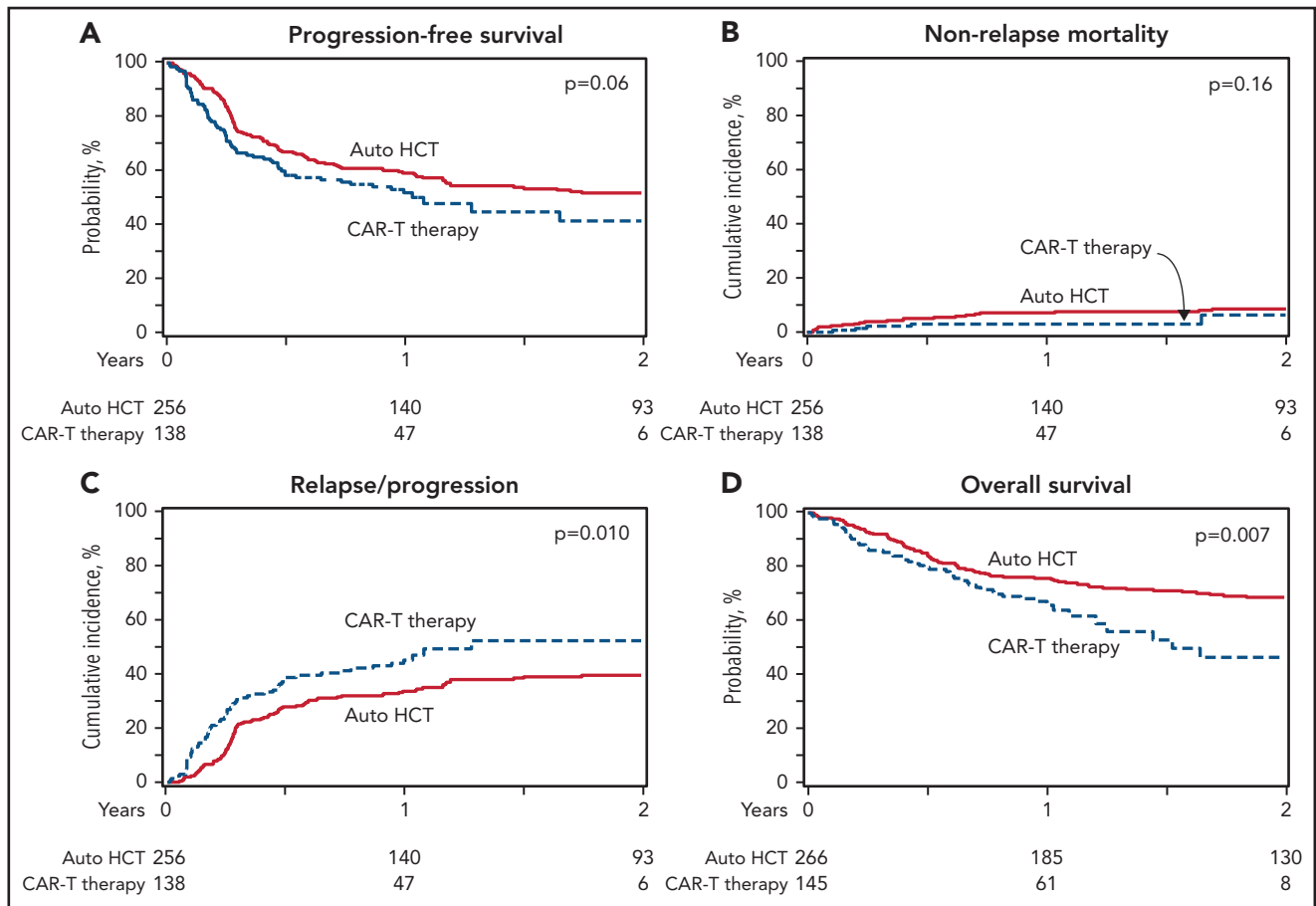
Figure 1. Auto-HCT vs CAR-T in patients with DLBCL in PR (all patients). (A) Progression-free survival. (B) Nonrelapse mortality. (C) Progression/relapse. (D) Overall survival.

Definitions and endpoints

Disease status before auto-HCT or CAR-T and determination of the PR status was defined per Lugano working group classification and determined by local radiologic assessments at transplant or immunotherapy centers.[9] The primary endpoint of the study was PFS, defined as the time from either auto-HCT or CAR-T to relapse or death from any cause. Secondary endpoints: overall survival (OS) defined as the time from treatment to death of any cause, the cumulative incidence of nonrelapse mortality (NRM) defined as death without preceding disease progression, the cumulative incidence of relapse/progression defined as the time from treatment to relapse or disease progression and hematopoietic recovery. For CAR-T patients, the cumulative incidence of cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) were calculated. CRS and ICANS were graded using the American Society of Transplant and Cellular Therapy grading criteria.[11] Subgroups analyses were performed for (1) patients with an available PET scan before auto-HCT or CAR-T and (2) patients who received ≤2 or >2 prior lines of treatment.

Statistical analysis

We compared the baseline characteristics between the auto-HCT and CAR-T cohorts using the Kruskal-Wallis test for continuous variables and the Pearson χ^2 test for categorical variables after ignoring the missing data. The Kaplan-Meier estimator and the log-rank test were used to compare the OS and PFS of the auto-HCT and CAR-T cohorts. The cumulative incidence function with Gray's test was used to compare the hematopoietic recovery, NRM, and relapse/progression rates in the 2 cohorts to account for competing events. We used the Cox proportional hazard model for PFS and OS; and the proportional cause-specific hazards model for NRM and relapse/progression to compare the 2 cohorts. The variables included in the regression model were: age (continuous and by decade), Karnofsky performance status (≥90 vs <90 vs missing), refractoriness to first-line treatment, number of lines of prior therapies, the interval between diagnosis and auto-HCT or CAR-T (≥1 year vs <1 year vs missing), size of the largest residual node at auto-HCT or CAR-T (<3 cm vs 3-5 cm vs >5 cm vs unknown). The forward stepwise selection was used to identify significant variables at a significance level of 0.05. Interactions between variables in the final regression model were also checked. Proportional hazards assumption was examined by testing covariates' time-varying effects. To confirm the regression analysis results further, we conducted propensity score matching. To calculate propensity scores, we used multiple imputations using R package smcfcs and Rubin's rule to handle missing covariates.[12-14] Using calculated propensity scores, we matched the auto-HCT and CAR-T cohorts using R package MatchIt with a 1:2 matching ratio for CAR-T and auto-HCT.[15] The marginal model was used to handle correlation within matched pairs.[16] All statistical analyses were

Table 2. Univariable analysis of outcomes in patients treated with auto-HCT or CAR-T while in a PR

Outcomes	Auto-HCT (N = 266)		CAR-T (N = 145)		P value
	N eval	Prob (95% CI)	N eval	Prob (95% CI)	
Nonrelapse mortality	256		138		.2*
100 d		4 (2-7)		2 (0-5)	.3†
1 y		7 (4-11)		3 (1-6)	.05†
2 y		9 (5-13)		6 (1-16)	.6†
Progression/relapse	256		138		.01*
1 y		34% (28-40)		45% (37-54)	.03†
2 y		40% (33-46)		52% (41-63)	.05†
Progression-free survival	256		138		.1*
1 y		59% (53-65)		52% (43-61)	.2†
2 y		52% (46-58)		42% (30-53)	.1†
Overall survival	266		145		.01*
1 y		76% (70-81)		67% (59-75)	.1†
2 y		69% (63-74)		47% (33-60)	.004†

N eval, number evaluated; Prob, probability.

*Overall P values from the log-rank test (PFS and OS) and Gray's test (NRM and progression/relapse).

†P values from the Wald test given time.

performed using SAS version 9.4 (SAS Institute, Cary, NC) and R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

We identified 411 patients with DLBCL who received either an auto-HCT (n = 266) or CAR-T therapy (n = 145) while in a PR by computed tomography or PET scan during the study period. Baseline characteristics are summarized in Table 1. There was no significant difference in age (median 58 vs 60 years; P = .07), performance status (Karnofsky ≥90: 51% vs 39%; P = .09), and the proportion of patients who had a pretreatment PET scan (83% vs 87%; P = .36) for disease assessment. Auto-HCT patients had received fewer median lines of prior therapies (median 2 vs 3; P < .001). Although not statistically significant, fewer patients in the auto-HCT group had the largest pretreatment residual node measuring >5 cm (29% vs 41%; P = .05). Twenty-three patients (16%) received bridging therapy between leukapheresis and lymphodepletion in the CAR-T cohort. Disease response was reassessed in 15 of them following bridging, and none converted their PR to CR following bridging. Fourteen patients received CAR-T therapy after auto-HCT relapse.

Univariable analysis

The 2-year PFS was 52% (95% confidence interval [CI], 46-58) in the auto-HCT group and 42% (95% CI, 30-53) in the CAR-T group (P = .1) (Figure 1A; Table 2). NRM rates were not different between the 2 cohorts with a 100-day cumulative incidence of NRM of 4% (95% CI, 2-7) vs 2% (95% CI, 0-5) (P = .3) in auto-HCT and CAR-T patients, respectively (Figure 1B). The cumulative incidence of relapse/progression was lower with auto-HCT at 1 year (34% [95% CI, 28-40] vs 45% [95% CI, 37-54]; P = .03) and 2 years (40% [95% CI, 33-46] vs 52% [95% CI,

41-63]; P = .05]) (Figure 1C). The 2-year OS rate was higher in the auto-HCT group compared with the CAR-T (69% [95% CI, 63-74] vs 47% [95% CI, 33-60]; P = .004) (Figure 1D).

Information about probabilities of hematopoietic recovery in both cohorts and CRS and ICANS in the CAR-T cohort are summarized in supplemental Table 1.

Subgroup analyses

In a subgroup analysis of patients with an available PET scan before auto-HCT (n = 222) or CAR-T (n = 126), there was no difference the 2-year PFS rate (54% [95% CI, 47-61] vs 43% [95% CI, 32-55]; P = .1) but consolidation with auto-HCT was associated with a lower 2-year cumulative incidence of relapse/progression (39% [95% CI, 32-46] vs 54% [95% CI, 42-66]; P = .03) and an improved 2-year OS rate (71% [95% CI, 65-77] vs 49% [95% CI, 34-63]; P = .006). There was no difference in the 100-day NRM (3% [95% CI, 1-5] vs 2% [95% CI, 0-5]; P = .5) (Table 3). When the subgroup analysis only included patients with ≤2 prior lines of therapy, there was no difference in the 1-year PFS (59% [95% CI, 52-67] vs 65% [95% CI, 49-79]; P = .5), cumulative incidence of relapse/progression (33% [95% CI, 26-41] vs 35% [95% CI, 21-51]; P = .8) or OS (76% [95% CI, 69-82] vs 77% [95% CI, 62-89]; P = .9) but auto-HCT (n = 172) was associated with a higher 100-day NRM compared with CAR-T (n = 42) (4% vs 0; P = .01) (Figure 2; supplemental Table 2). Focusing on patients with more than 2 prior lines of treatment, auto-HCT group (n = 89) had a superior OS at 2 years (63% [95% CI, 53-73] vs 44% [95% CI, 28-60]; P = .04) but there was no difference in the other endpoints (supplemental Tables 3 and 4). When analysis was limited to patients with early treatment failure (primary refractory disease or relapse within 12 months of diagnosis), auto-HCT (n = 186) vs CAR-T (n = 110) cohorts had no significant difference in 2-year PFS (53% [95% CI, 46-60] vs 40% [95% CI, 30-51]; P = .05), but auto-HCT group

Table 3. Subgroup univariable analysis of outcomes in patients treated with auto-HCT or CAR-T while in a PR in patients with known positive PET scan before treatment

Outcomes	Auto-HCT (N = 222)		CAR-T (N = 126)		P value
	N eval	Prob (95% CI)	N eval	Prob (95% CI)	
Nonrelapse mortality	215		119		.2*
100 d		3% (1-5)		2% (0-5)	.5†
1 y		6% (3-9)		3% (1-6)	.1†
2 y		7% (4-11)		3% (1-6)	.04†
Progression/relapse	215		119		.007*
1 y		33% (27-39)		46% (36-55)	.03†
2 y		39% (32-46)		54% (42-66)	.03†
Progression-free survival	215		119		.04*
1 y		61% (55-68)		52% (42-61)	.1†
2 y		54% (47-61)		43% (32-55)	.1†
Overall survival	222		126		.005*
1 y		79% (73-84)		69% (60-77)	.06†
2 y		71% (65-77)		49% (34-63)	.006†

N eval, number evaluated; Prob, probability.
*Overall P values from the log-rank test (PFS and OS) and Gray's test (NRM and Progression/relapse).
†P values from the Wald-test given time.

had lower relapse/progression rate (38% [95% CI, 31-45] vs 56% [95% CI, 45-67]; P = .006) and superior OS (66% [95% CI, 59-73] vs 40% [95% CI, 26-56]; P = .003) compared with the CAR-T group at 2 years.

Multivariable regression analysis

In the multivariable regression analysis of outcomes, there was no significant difference between the 2 cohorts in terms of PFS (hazard ratio [HR] =1.33 [95% CI, 0.98-1.80]; P = .06) and NRM (HR = 0.49 (95% CI, 0.18-1.32]; P = .16) but treatment with CAR-T was associated with a significantly higher risk of relapse/progression (HR 1.49 [95% CI, 1.08-2.05]; P = .01) and mortality (HR = 1.63 [95% CI, 1.14-2.33]; P = .008) (Table 4). We performed additional analysis after propensity score matching of the 2 cohorts (supplemental Table 5), and the HRs of primary and secondary endpoints were directionally consistent with the overall multivariate analysis, although the associations were no longer statistically significant (supplemental Table 6).

Cause of death

During the follow-up, 91 patients (34%) from the auto-HCT group and 52 (36%) from the CAR-T group died. The primary disease was the most common cause of mortality in both groups accounting for 74% and 75% of deaths in the auto-HCT and CAR-T groups, respectively. Other common causes were infections (6%) and organ failure (4%) in the auto-HCT group and infections (4%), cytokine release syndrome (4%), organ failure (4%), and malignancies (4%) in the CAR-T group.

Discussion

In this retrospective analysis using the CIBMTR registry, we compared the outcomes of patients with DLBCL treated with auto-HCT or CAR-T therapy while in a PR after the last therapy line.

Our results indicate similar PFS but a lower risk of relapse and a superior OS with auto-HCT. These data support the role of auto-HCT as standard of care in transplant-eligible patients with relapsed DLBCL that achieve at least a PR as the best response to salvage therapy but more data are needed to answer this question in patients with fewer lines of salvage therapy.

The introduction of CAR-T therapy as a therapeutic option for patients with relapsed DLBCL has been a major advancement in lymphoma treatment. Long-term remissions are achieved in 30% to 40% of patients receiving CAR-T therapy according to the clinical trial data and in the real-world setting.[17-19] This outstanding efficacy in a patient population with historically poor outcomes has led to increased utilization of CAR-T treatment, including in DLBCL patients who achieve only a PR after salvage attempt, for whom 1 recommended treatment strategy continues to be an auto-HCT per published guidelines.[20] In fact, the efficacy of auto-HCT has been recently confirmed in another CIBMTR analysis showing a 41% 5-year PFS in patients in PET-positive PR receiving an auto-HCT regardless of the timing of initial relapse/refractoriness consistent with the previous reports.[8,21]

Three ongoing randomized controlled trials (A Study to Compare the Efficacy and Safety of JCAR017 to Standard of Care in Adult Subjects With High-risk, Transplant-eligible Relapsed or Refractory Aggressive B-cell Non-Hodgkin Lymphomas [TRANSFORM] NCT03575351; Efficacy of Axicabtagene Ciloleucel Compared to Standard of Care Therapy in Subjects With Relapsed/Refractory Diffuse Large B Cell Lymphoma [ZUMA-7] NCT03391466; and Tisagenlecleucel in Adult Patients With Aggressive B-cell Non-Hodgkin Lymphoma [NCT03570892]) are comparing the efficacy and safety of each of the 3 approved CAR-T products (Lisocabtagene Maraleucel, axi-cel, and tisa-cel) with the standard of care (ie, salvage chemotherapy followed by
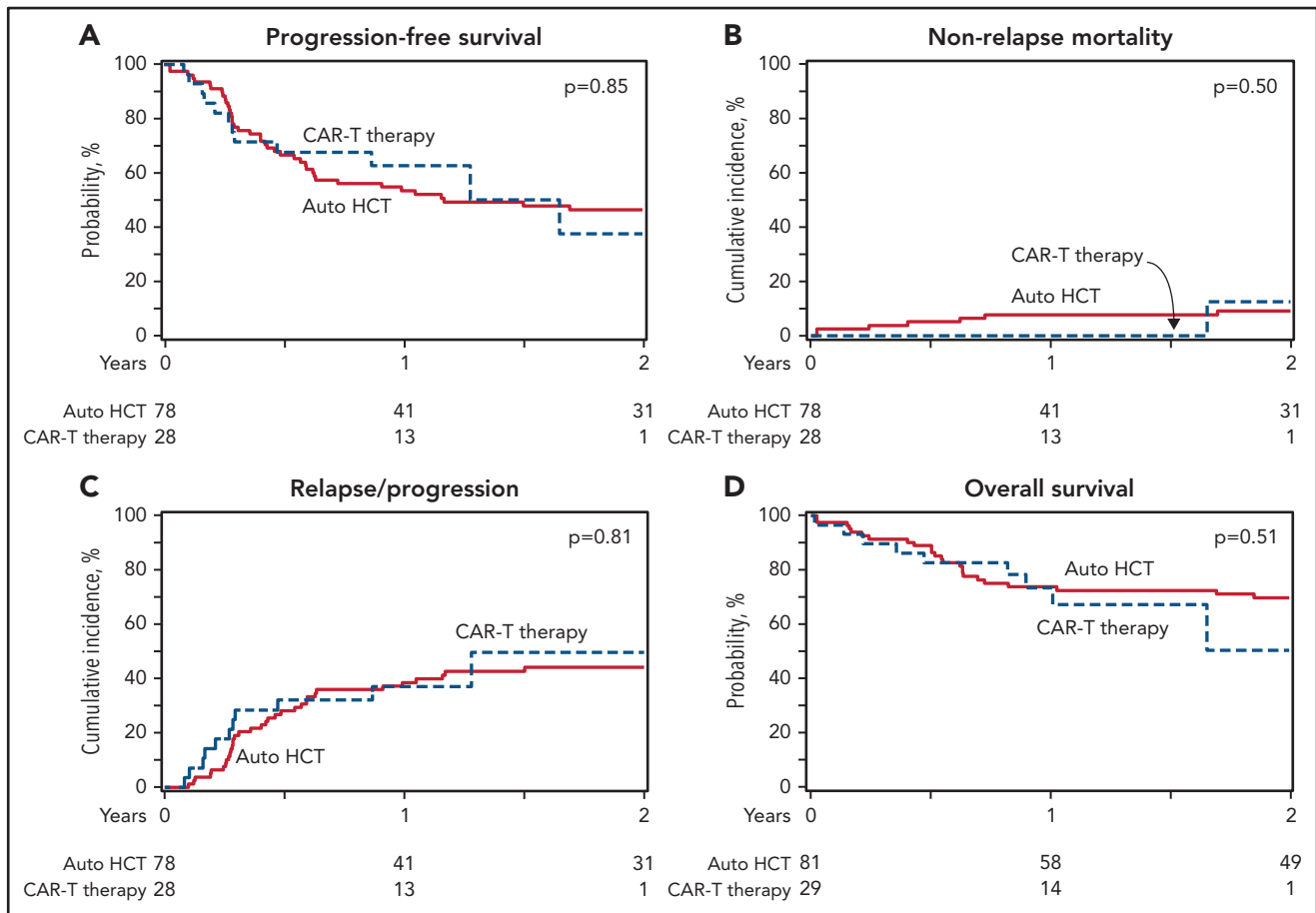
Figure 2. Auto-HCT vs CAR-T in patients with DLBCL in PR (patients with ≤2 prior lines of treatment). (A) Progression-free survival. (B) Nonrelapse mortality. (C) Progression/relapse. (D) Overall survival.

auto-HCT) in the relapsed/refractory setting. All 3 trials only included patients with primary refractory or early relapsed (within 12 months) disease and excluded those who received any second-line systemic treatment. From the 3 studies, the available information is from press releases of the TRANSFORM and ZUMA-7 studies in June 2021, which indicated an event-free survival benefit with liso-cel or axi-cel over standard of care in patients with DLBCL with early treatment failure.[22,23] However, although informative, these studies will not address the clinical question that we aimed to answer with this analysis because this study specifically included patients in a PR after salvage treatment. In addition, the result of these trials may not be applicable to patients with DLBCL not fulfilling early relapse criteria.

Rather than identifying a "winner" approach, our findings help determine the optimal treatment sequence for this patient population. Given the established clinical efficacy of auto-HCT in this setting and with the complexity and the financial burden of using CAR-T therapy, especially in the absence of data suggesting its superiority when compared with the standard of care, the logical treatment sequence will include using auto-HCT first, knowing the proven efficacy of CAR-T in the posttransplant failure setting. Because auto-HCT remains to be a major treatment modality for DLBCL, continued support for ongoing and planned studies to further improve the efficacy of this effective treatment is necessary. Such studies would incorporate novel

targeted agents to the auto-HCT either by augmenting the conditioning regimen or as a maintenance strategy.[24]

Our analysis has inherent limitations of a retrospective study. Using the registry data, the cohorts are not entirely balanced, and we were limited in assessing the clinical decision process behind selecting each treatment modality. Another important limitation relates to the subjectivity of PR definition, especially in the nonclinical trial setting. With the current definition of a PR based on the standard response assessment guidelines, a wide range of patients with various tumor bulk and different levels of chemo-responsiveness could have potentially been included in this category. By including the pretreatment largest node size in our models, we attempted to some degree control for this limitation, but the possibility of residual confounder effect cannot be ruled out especially given the higher numerical percentage of patients with >5 cm lymph node.[25-27] We observed consistent results in our subgroup analysis focusing on patients with an available PET scan before treatment mitigating the risk effect modification by the diagnostic modality.[21] Also, there was no independent centralized reading of the scans to confirm the reported PR response by the transplant center. Patients in the auto-HCT cohort were included from a longer period (2013-2019) compared with the CAR-T patients (2018-2019). This approach is justified given the comparable auto-HCT outcomes before and after 2018 (data not shown). Comparison between

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Table 4. Multivariable regression analysis of outcomes in patients treated with auto-HCT or CAR-T while in a PR

Outcomes	N	HR	95% CI lower limit	95% CI lower limit	*P* value
Nonrelapse mortality					
Age, y					
<60	212	1.00			
≥60	182	2.92	1.31	6.50	.009
Main effect					
Auto-HCT	256	1.00			
CAR-T	138	0.49	0.18	1.32	.16
Progression/relapse					
Main effect					
Auto-HCT	256	1.00			
CAR-T	138	1.49	1.08	2.05	.01
Progression-free survival					
Main effect					
Auto-HCT	256	1.00			
CAR-T	138	1.33	0.98	1.80	.06
Overall survival					
Main effect					
Auto-HCT	266	1.00			
CAR-T	145	1.63	1.14	2.33	.008

Variables included in the multivariable analysis: age (continuous by decade), Karnofsky performance score (≥90 vs <90 vs missing), refractoriness to first line, lines of prior treatment, interval between diagnosis and auto-HCT or CAR-T (≥1 y vs <1 y vs missing), largest node at auto-HCT or CAR-T (<3 cm vs 3-5 cm vs >5 cm vs unknown).

CAR-T and auto-HCT was made using propensity score matching as well. Although the effect on disease relapse/progression and mortality was directionality consistent with the primary analysis, it was not statistically significant. This subset analysis reduced the sample size, which likely affected the power to detect statistical significance. The observed difference was mainly observed in patients with ≥2 prior lines of treatment. This cutoff was used for subgroup analysis, given the implications in clinical practice. Although lack of statistical significance in patients with <2 prior lines of treatment warrants further attention and ideally prospective trials in that group, the small number of patients in this subgroup analysis limits our ability for making a strong conclusion, particularly because we did not observe an interaction (effect modification) between the number of prior treatment lines and treatment modality and outcomes. Patients in the CAR-T group were more heavily pretreated and it is possible that the CAR-T may show improved efficacy in patients with fewer lines of prior treatment Last, we only included patients treated with axi-cel to reduce the heterogeneity given the small number of patients treated with tisa-cel in the registry, fulfilling eligibility criteria for this study at the time of the analysis.

In summary, for patients with DLBCL who achieve a PR after salvage chemotherapy, treatment with auto-HCT was associated with a similar PFS rate, but led to a lower incidence of relapse and an improved OS compared with CAR-T in this analysis. We anxiously await full results of randomized phase 3 data to inform the optimal second-line therapy. However, regardless of the outcome of those studies, our findings will have clinical implications. We anticipate that even if CAR-T cell therapy is widely viewed as the superior treatment option (based on the press release TRANSFORM and ZUMA-7 studies), there will still be patients who will receive chemotherapy after relapse for many reasons: (1) not meeting the eligibility criteria; (2) lack of immediate access to CAR-T therapy; or (3) simply based on patient or physician preferences. These data will inform decisions if those patients achieve a PR. Last, these data highlight the need for a prospective randomized trial for patients with chemosensitive disease and in a PR after salvage therapy comparing CAR-T to the standard of care.

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Authorship

Contribution: M.S. and M.H. conceived and designed the study; Y.C. and M.H. collected and assembled data; Y.C., M.H., and K.W.A. provided data analysis; all authors interpreted the data; M.S. and M.H. prepared the first draft prepared; and all authors helped revised the manuscript.

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