Autologous hematopoietic cell transplantation in diffuse large B-cell lymphoma after three or more lines of prior therapy: evidence of durable benefit

While most patients with diffuse large B-cell lymphoma (DLBCL) are cured with initial chemoimmunotherapy, one-third of patients will have relapsed and/or refractory (r/r) disease after frontline treatment. Salvage combination chemoimmunotherapy followed by autologous hematopoietic cell transplantation (autoHCT), in patients achieving an objective response to cures less than half of such patients.[1,2] Most patients who undergo autoHCT do so after second line (2L) therapy, but some do so after having received three or more lines (3L+) of prior therapy. Data are lacking on the outcomes after autoHCT in patients with DLBCL in the 3L+ setting. Although CD19-directed chimeric antigen receptor T-cell (CAR-T) therapy is being increasingly used in the 3L+ setting with curative intent,[3-5] this topic remains relevant given issues with access to CAR-T both in the US[6] and worldwide, particularly in low and middle income countries.[7] Here we report outcomes after autoHCT in the subset of patients with DLBCL who received 3L+ of systemic therapy in a Center for International Blood and Marrow Transplant Research (CIBMTR) registry analysis.

The CIBMTR is a collaborative research program managed by the Medical College of Wisconsin and the National Marrow Donor Program that collects data from more than 380 transplant centers worldwide. Participating sites are required to report detailed data on both autologous and allogeneic HCT with frequent updates gathered during the longitudinal follow-up of transplant patients, and the compliance is monitored by on-site audits. Computerized checks for discrepancies, physicians' review of submitted data, and on-site audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. The Medical College of Wisconsin and National Marrow Donor Program Institutional Review Boards approved this study.

Patients with DLBCL (aged ≥18 years) who received autoHCT between 2003 and 2017 with a preparative regimen of either BEAM (carmustine, etoposide, cytarabine, melphalan) or R-BEAM (rituximab with BEAM) conditioning after 3L+ therapy were included in this analysis. All patients received rituximab-containing, anthracycline-based frontline therapy. Patients who received a bone marrow graft, with chemorefractory disease after salvage therapy, and with active central nervous system involvement prior to autoHCT were excluded. Patients with transformed DLBCL evolving from prior indolent lymphoma were also excluded. Chemosensitive disease was defined as achieving either a complete remission (CR) or partial remission (PR) to salvage treatment. Response to frontline chemoimmunotherapy and disease status at autoHCT were determined by each center using the International Working Group criteria.[8,9] Early chemoimmunotherapy failure was defined as not achieving a CR after frontline chemoimmunotherapy or relapse/progression within 1 year of initial diagnosis.[10]

The primary endpoint was OS. Death from any cause was considered an event and surviving patients were censored at last follow-up. Secondary outcomes included non-relapse mortality (NRM), relapse/progression, and progression-free survival (PFS). NRM was defined as death without preceding evidence of lymphoma progression/relapse; relapse was considered a competing risk. Relapse/progression was defined as progressive lymphoma after autoHCT or lymphoma recurrence after a CR; NRM was considered a competing risk. For PFS, a patient was considered a treatment failure at the time of progression/relapse or death from any cause. Patients alive without evidence of disease relapse or progression were censored at last follow-up. All outcomes were calculated relative to the autoHCT date.

The study cohort was divided according to remission status at the time of autoHCT (CR *vs.* PR). Patient-, disease- and transplant-related variables were compared between the two cohorts using the Chi-square test for categorical variables and the Wilcoxon two-sample test for continuous variables. The distribution of OS and PFS were estimated using the Kaplan-Meier method. Cumulative incidence method was used to estimate NRM, relapse/progression while accounting for competing events. The Cox proportional hazards model for PFS and OS and the cause-specific hazards model for relapse and NRM were used to identify prognostic factors using forward stepwise variable selection. No covariates violated the proportional hazards assumption. No significant interactions between the main effect and significant covariates were found. No center effects were found based on the score test of homogeneity.[11] Results were reported as hazard ratio (HR), 95% confidence interval (CI) for HR and *P*-value. The adjusted probabilities for each outcome were calculated based on the final regression model. Covariates with a *P*-value <0.05 were considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

A total of 285 patients met the inclusion criteria; over the same interval, 577 patients in the dataset who otherwise met the inclusion criteria had undergo autoHCT after receiving two or fewer lines of prior therapy. Median age was 60 years (range, 19-80 years), 60% were male, 80% were Caucasian, and 63% had early chemoimmunotherapy failure. Eighty percent received BEAM conditioning and 20% received R-BEAM. Details regarding the 3L treatment regimen are included in the *Online Supplementary Table S3*. Baseline characteristics are shown in Table 1. 5-year OS and PFS were 51% (95% CI: 44-57) and 38% (95% CI: 32-55), respectively. Adjusted 1-year, 3-year, and 5-year PFS and OS are shown in Table 2. Patients in CR at autoHCT had a higher 1-year OS (84% *vs.* 63%, *P*<0.001) and PFS (69% *vs.* 48%, *P*<0.001) in contrast to patients in PR, with the difference in OS persisting at 3 years (OS 64% *vs.* 50%, *P*=0.02). There was a trend towards improved 5-year OS for patients in CR (56% *vs.* 45%, *P*=0.06), whereas 5-year PFS did not differ significantly between the two cohorts (42% *vs.* 34%, *P*=0.18).

The 1- and 5-year incidence of relapse/progression for all patients was 36% (95% CI: 31-42) and 50% (95% CI: 43-56), respectively. Patients in CR had a significantly lower 1-year incidence of relapse/progression (26% *vs.* 47%, *P*<0.001); however, there was no difference found in relapse/progression at 5 years between the two cohorts (45% *vs.* 54%, *P*=0.14). The 1-year and 5-year NRM were 5% (95% CI: 3-8) and 12% (95% CI: 9-17), respectively with no difference identified between patients in CR and those in PR. A graph of outcomes stratified by disease status at autoHCT is provided in Figure 1.

A multivariable regression model was constructed to

evaluate for association between disease status at autoHCT (CR *vs.* PR), baseline covariates, and NRM, relapse, PFS, and OS; covariates are listed in the *Online Supplementary Table S1*. PR at autoHCT was associated with significantly increased risk of relapse (HR 1.59, 95% CI: 1.13-2.24, *P*=0.008), inferior PFS (HR 1.46, 95% CI: 1.08-1.97, *P*=0.01), and OS (HR 1.55, 95% CI: 1.12-2.15, *P*=0.009, *Online Supplementary Table S2*). Causes of death were analyzed for the 144 patients who died. Overall, 61% (n=88) died from DLBCL, whereas the second leading cause of death was secondary malignancy (10%).

We have found in our registry analysis that autoHCT performed in the 3L+ setting for DLBCL is feasible and effective with a 5-year PFS of 41% and 35% in patients who achieved CR and PR, respectively, prior to autoHCT. Multivariate regression analyses demonstrated that CR at the time of autoHCT was associated with less relapse and improved PFS and OS. These data suggest that autoHCT still may play a role in the 3L+ setting in DLBCL for patients who demonstrate an objective response to a second salvage. In fact, a substantial percentage of 3L+ patients in PR at autoHCT experienced durable disease control. This finding is in keeping with a

Table 1. Baseline characteristics of patients receiving BEAM conditioning regimen and autologous hematopoietic cell transplantation for diffuse large B-cell lymphoma during 2003-2017 (>=three prior lines of treatment)

	All patients	CR	PR	*P*-value
Number of patients	285	154	131	
Patient age				0.28
Median (range), y	60 (19-80)	60 (20-80)	59 (19-77)	0.22
≥ 65 y, n (%)	85 (30)	46 (30)	39 (30)	
Males	170 (60)	92 (60)	78 (60)	0.97
Patient race				0.76
Caucasian	229 (80)	124 (80)	105 (80)	
African American	28 (10)	15 (10)	13 (10)	
Other*	18 (6)	11 (7)	7 (5)	
Missing	10 (4)	4 (3)	6 (5)	
Karnofsky Performance Score				0.02
≥ 90	140 (49)	87 (57)	53 (40)	
Missing	12 (4)	7 (4)	5 (4)	
Stage at diagnosis				
Stage III-IV	199 (70)	106 (69)	93 (71)	0.66
Missing	17 (6)	11 (7)	6 (5)	
LDH				
Elevated at diagnosis	39 (14)	25 (16)	14 (11)	0.39
Missing	182 (64)	95 (62)	87 (66)	
Bone marrow involvement at diagnosis				0.07
No	202 (71)	102 (66)	100 (76)	0.22
Missing	15 (5)	7 (5)	8 (6)	
Extranodal involvement at diagnosis				
Yes	181 (64)	105 (68)	76 (58)	0.22
Missing	15 (5)	7 (5)	8 (6)	
Time from diagnosis to HCT, median (range), mo	(5-172)	23 (6-140)	17 (5-172)	0.01
Early chemoimmunotherapy failure				
Yes	179 (63)	86 (56)	93 (71)	0.02
Missing	6 (2)	5 (3)	1 (1)	
Primary refractory after first line of therapy				
Yes	119 (42)	46 (30)	73 (56)	< 0.001
Missing	19 (7)	14 (9)	5 (4)	
Number of prior lines of therapy				
3	217	126	91	0.01
>3	68	28	40	
Conditioning regimen				0.32
BEAM	227 (80)	126 (82)	101 (77)	
Rituximab-BEAM	58 (20)	28 (18)	30 (23)	
Year of transplant				0.61
2003-2007	98 (34)	49 (32)	49 (37)	
2008-2012	99 (35)	56 (36)	43 (33)	
2013-2017	88 (31)	49 (32)	39 (30)	
Median follow-up of survivors (range), mo	72 (4-145)	72 (6-145)	72 (4-143)	

Unless otherwise noted, data are n (%). BEAM: carmustine, etoposide, cytarabine, and melphalan; HCT: hematopoietic stem cell transplantation; DLBCL: diffuse large B-cell lymphoma; LDH: lactate dehydrogenase; CR: complete remission; PR: partial remission; y: years, mo: months. *Other race: CR: 11 Asian; PR: 5 Asian; 1 American Indian or Alaska Native; 1 Native Hawaiian or Other Pacific Islander.

recent CIBMTR analysis that patients with a PR prior to autoHCT had a 5-year PFS of 41%.[12] As such, patients with chemosensitive disease, particularly those who attain a CR, should not be denied the opportunity for curative intent treatment with autoHCT solely due to the number of prior lines of therapy.

We acknowledge a number of limitations with this analysis including its retrospective design as well as that these data pertain only to patients who respond to salvage therapy, and many patients do not.[13] Registry data show that the number of patients who undergo autoHCT in the 3L+ setting is less than those who do so after two lines of therapy.[10,14] Of the patients in the CORAL study who did not respond to second-line therapy, only 39% responded to 3L therapy and 28% of patients ultimately proceeded to autoHCT.[15] Furthermore, many novel therapies for DLBCL have been approved recently including multiple targeted treatments as well as three separate CAR-T products.[3-5] CAR-T therapy has profoundly impacted the care of DLBCL given its ability to induce durable remissions even in the setting of chemorefractory disease. Although only approved in the third line setting at present, randomized trials of CAR-T compared to salvage chemoim-

Table 2. Adjusted outcomes.

Outcomes	All patients (N = 285)	CR (N = 154)	PR (N = 131)	*P*-Value
Non-relapse mortality (range)				
1-year	5 (3-8)	5 (2-9)%	5 (1-8)%	0.68
3-year	11 (8-15)	12 (7-18)%	9 (4-14)%	0.40
5-year	12 (9-17)	13 (8-19)%	12 (6-17)%	0.65
Relapse/progression (range)				
1-year	36 (31-42)	26 (19-33)%	47 (39-56)%	<0.001
3-year	44 (38-50)	38 (30-46)%	51 (42-59)%	0.03
5-year	50 (43-56)	45 (37-53)%	54 (45-63)%	0.14
Progression-free survival (range)				
1-year	59 (53-64)	69 (61-76)%	48 (39-56)%	<0.001
3-year	45 (39-51)	50 (42-59)%	40 (31-48)%	0.08
5-year	38 (32-44)	42 (34-51)%	34 (26-43)%	0.18
Overall survival (range)				
1-year	74 (69-79)	84 (79-90)%	63 (55-71)%	<0.001
3-year	57 (51-63)	64 (56-72)%	50 (42-59)%	0.02
5-year	51 (44-57)	56 (48-65)%	45 (36-54)%	0.06

Data are percentage probability (95% confidence interval). CR: complete remission; PR: partial remission.

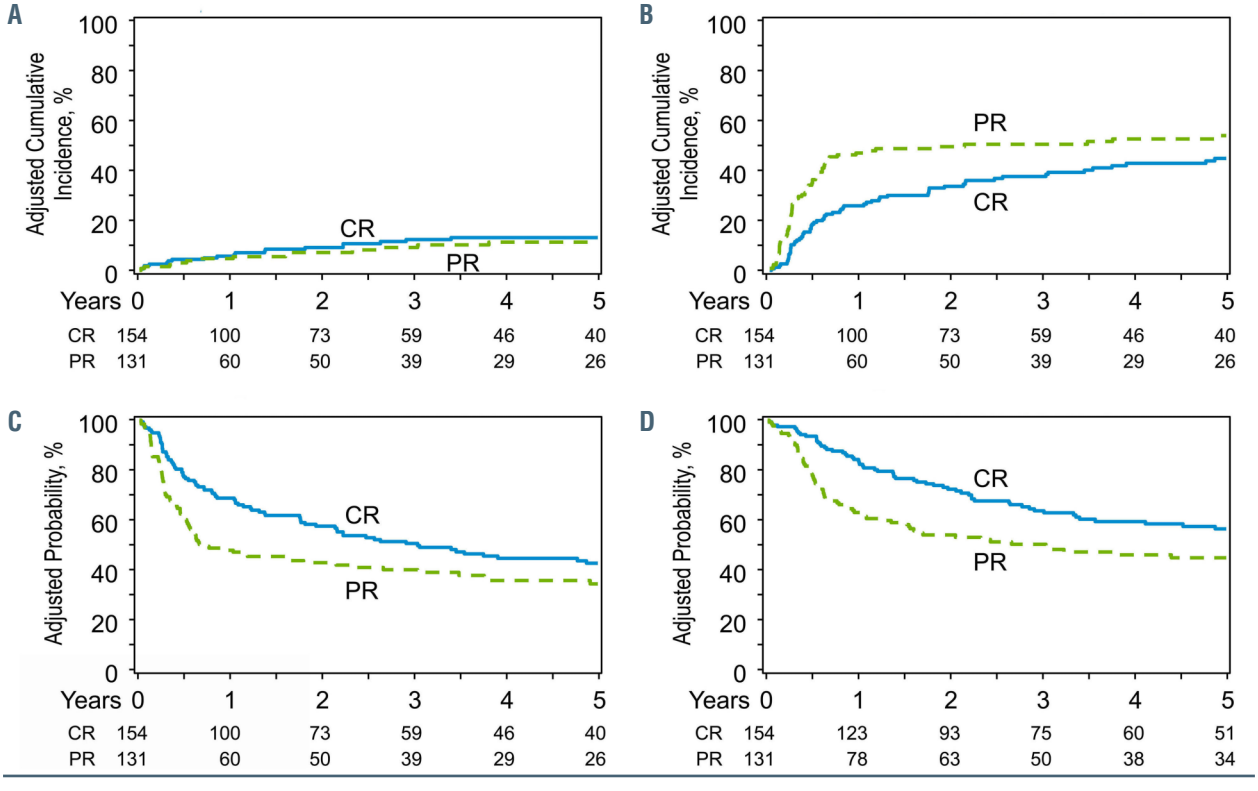

Figure 1. Post- autologous hematopoietic cell transplantation (autoHCT) outcomes stratified by pre-autoHCT disease status (complete response *vs.* partial remission). (A) Non-relapse mortality, (B) relapse/progression, (C) progression-free survival and (D) overall survival. CR: complete remission; PR: partial remission.

munotherapy/autoHCT as second line therapy are being conducted (TRANSFORM, clinicaltrials gov. Identifier: NCT03575351; ZUMA-7, clinicaltrials gov. Identifier: NCT03391466, and BELINDA, clinicaltrials gov. Identifier: NCT03570892) with potential practice-changing implications. The number of patients who received novel therapies including CAR-T prior to autoHCT in this analysis is likely low as the first commercial CAR-T product was approved in late 2017 and the first targeted therapy for relapsed DLBCL in 2019 (polatuzumab vedotin-piiq).

Nonetheless, the retrospective data presented here suggest that autoHCT still has a role in r/r chemosensitive DLBCL even in later lines of therapy. If CAR-T ultimately becomes standard second line therapy, these data may serve as a benchmark for autoHCT outcomes in patients with 3+ prior lines of chemotherapy. Additionally, it would support offering an autoHCT in patients in the 3L+ setting in countries where CAR-T may not be available.

Matthew Mei,[1] Mehdi Hamadani,[2] Kwang W. Ahn,[3,4] Yue Chen,[4] Mohamed A. Kharfan-Dabaja,[5] Craig Sauter[2] and Alex F. Herrera[1]

[1]Department of Hematology and Hematopoietic Cell Transplantation, City of Hope, Duarte, CA; [2]BMT & Cellular Therapy Program, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI; [3]Division of Biostatistics, Medical College of Wisconsin, Milwaukee, WI; [4]Center for International Blood and Marrow Transplant Research, Milwaukee, WI and [5]Division of Hematology-Oncology and Blood and Marrow Transplantation Program, Mayo Clinic, Jacksonville, FL, USA

Correspondence: MEHDI HAMADANI mhamadani@mcw.edu

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