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Outcomes of rituximab-BEAM vs BEAM conditioning regimen in patients with diffuse large B-cell lymphoma undergoing autologous transplantation.

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Abstract

Background—Although rituximab-based high-dose therapy is frequently used in DLBCL patients undergoing autologous hematopoietic cell transplantation (auto-HCT), data supporting the benefit are not available. Herein, we report the impact of rituximab-based conditioning on auto-HCT outcomes in DLBCL.

Methods—Using the CIBMTR registry, 862 adult DLBCL patients undergoing auto-HCT between 2003–2017 using BEAM (BCNU, etoposide, cytarabine, melphalan) conditioning regimen were included. All patients received frontline rituximab (R)-containing chemoimmunotherapy and had chemosensitive disease pre-HCT. Early chemoimmunotherapy failure (ECitF) was defined as not achieving a complete remission (CR) post-frontline chemoimmunotherapy, or relapse within 1-year of initial diagnosis. Primary outcome was overall survival (OS).

Results—The study cohort was divided into 2 groups; BEAM (n=667) and R-BEAM (n=195). On multivariate analysis, no significant difference was seen in OS (P=0.83) or progression-free survival (PFS) (P=0.61) across the two cohorts. No significant association between the use of rituximab and risk of relapse (P=0.15) or non-relapse mortality (P=0.12) was observed. Variables independently associated with lower OS included older age at auto-HCT (P<0.001), absence of CR at auto-HCT (P<0.001) and ECitF (P<0.001). Older age (P<0.0002) and non-CR pre-HCT (P<0.0001) were also associated with inferior PFS. There was no significant difference in early infectious complications between the two cohorts.

Conclusion—In this large registry analysis of DLBCL patients undergoing auto-HCT, the addition of rituximab to the BEAM conditioning regimen had no impact on transplantation outcomes. Older age, absence of CR pre auto-HCT and ECitF were associated with inferior survival.

Condensed Abstract

Using CIBMTR registry data, we demonstrate that in DLBCL patients undergoing auto-HCT, the addition of rituximab to the BEAM conditioning regimen had no impact on survival outcomes after transplantation.

Keywords

diffuse large B-cell lymphoma; autologous transplantation; rituximab; BEAM; chemoimmunotherapy

Introduction

Rituximab has revolutionized the treatment landscape of B-cell non-Hodgkin lymphomas (NHL). Integrating rituximab into upfront and subsequent lines of treatment has improved response rates, progression-free and overall survival (OS) in B-cell NHL[1–4]. In randomized clinical trials, the addition of rituximab to CHOP (cyclophosphamide, adriamycin, vincristine and prednisone) chemotherapy resulted in superior complete response (CR) rate, event-free survival (EFS) and OS compared to CHOP in both young (18–60 years) and elderly (60–80 years) patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL)[1, 5].

The benefit of combining rituximab with autologous hematopoietic cell transplantation (auto-HCT) conditioning regimens is not well defined and no randomized clinical trials have explored this issue. Retrospective studies evaluating the integration of rituximab with conditioning regimens for auto-HCT in B-cell NHL have produced conflicting results[6–8]. Flohr et al. reported encouraging response rates when rituximab was administered on days −10 and −3 with various conditioning regimens for auto-HCT[6]. Unfortunately, in this study there was no non-rituximab control arm and multiple B-cell NHL histologies were included. The BMT CTN 0410 phase III trial found comparable outcomes between rituximab + BEAM (carmustine, etoposide, cytarabine and melphalan) and B-BEAM (iodine I-131 tositumomab + BEAM) in relapsed chemosensitive DLBCL[7]. As there was no BEAM-alone arm, the study does not explicitly address whether rituximab-BEAM (R-BEAM) offered any benefit over BEAM.

No studies evaluating the benefit of combining rituximab with BEAM conditioning regimen in patients with DLBCL have been reported to our knowledge. As efforts to reduce health care cost are mounting, it is imperative to determine if addition of an anti CD20 monoclonal antibody could produce improved outcomes in DLBCL post auto transplantation. This is more relevant in the modern-era, as rituximab containing regimens are standard-of-care in both upfront and salvage setting and the benefit of brief exposure to rituximab (in a largely rituximab exposed patient population) during auto-HCT conditioning remains to be proven.

Therefore, we conducted a retrospective study using the Center for International Blood and Marrow Transplant Research (CIBMTR) registry comparing the post auto-HCT outcomes between R-BEAM and BEAM in patients with DLBCL.

Methods

Data source

The CIBMTR is a collaborative research program managed by Medical College of Wisconsin (MCW) and The National Marrow Donor Program (NMDP) that collects data from more than 500-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 MCW and NMDP institutional review boards approved this study.

Patients

DLBCL patients age ≥18 years, who received an auto-HCT between 2003–2017 and reported to CIBMTR were included in this analysis. Conditioning for auto-HCT was limited to BEAM regimen, as rituximab was infrequently used with non-BEAM conditioning approaches. All patients received rituximab-containing chemoimmunotherapy in the first-line setting and had chemosensitive disease prior to auto-HCT. Patients who received a bone marrow graft (n= 36), underwent non-rituximab containing frontline therapy (n=134) and those with active central nervous system involvement prior to auto-HCT (n= 5) were excluded.

Definitions and Endpoints:

Chemosensitive disease is defined as achieving either a CR or partial remission (PR) to treatment prior to transplant. Response to frontline chemoimmunotherapy and disease status prior to auto-HCT were determined using the International Working Group criteria[8,9]. Early chemoimmunotherapy failure was defined as not achieving a CR after first line of chemoimmunotherapy or relapse/progression within 1 year of initial diagnosis as previously reported[10,11].

Primary endpoint was OS. Death from any cause was considered an event and surviving patients were censored at last follow-up. Secondary outcomes included NRM, relapse/progression, and progression-free survival (PFS). NRM was defined as death without evidence of prior lymphoma progression/relapse; relapse was considered a competing risk. Relapse/progression was defined as progressive lymphoma after auto-HCT 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. Neutrophil engraftment is time to achieve an absolute neutrophil count (ANC)

>0.5 $\times 10^9$/L that is sustained for three consecutive days post-transplant. Platelet engraftment is time to achieve a platelet count of >20 $\times$ 10^9/L post transplant without any platelet transfusions for 7 consecutive days. Death prior to engraftment was considered a competing risk. All outcomes will be calculated relative to the transplant date.

Statistical Analysis:

All the endpoints were compared between R-BEAM and BEAM cohorts. 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 hematopoietic recovery, NRM, relapse/progression while accounting for competing events. Cox proportional hazard analysis was used to identify prognostic factors for relapse, NRM, PFS, and OS 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 effect was found based on the score test of homogeneity[12]. Results were reported as hazard ratio (HR), 95% confidence interval (CI) for HR and p-value. Covariates with a p value <0.05 were considered statistically significant. The variables considered in multivariate analysis are shown in Table 1S of supplemental appendix. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results:

Baseline Characteristics

The study population (n=862) was divided into 2 cohorts; BEAM (n=667) and R-BEAM (n=195). The baseline characteristics between the 2 groups were comparable (Table 1), with respect to patient age, gender, performance score, number of prior therapy lines, early chemoimmunotherapy failure and remission status prior to auto-HCT. Significantly more R-BEAM cohort patients had exposure to rituximab immediately before auto-HCT, either as part of last chemotherapy line before HCT or received rituximab with pre-transplant mobilization regiment (N=168; 86%) compared to the BEAM cohort subjects with similar pre-HCT rituximab exposure (n=504; 76%). The median follow up of survivors was 48 (range 1–171) months and 64 (range 3–142) months in the BEAM and the R-BEAM groups respectively.

Hematopoietic Recovery and Infectious Complications

The cumulative incidence of neutrophil recovery at day 30 was comparable between both groups 99% (95%CI=98–100%) and 98% (95%CI=96–100%) in the BEAM and the R-BEAM, respectively (Table 2). No difference was observed in the platelet recovery during the first 100 days: 97% (95%CI=96–98%) in the BEAM and 97% (95%CI=94–99%) in the R-BEAM respectively. In comparison to BEAM, addition of rituximab did not increase the risk of bacterial, viral or fungal infections during the first 100-day after auto-HCT (for details see Supplement Materials Table S2).

Non-relapse Mortality and Relapse/Progression

On univariate analysis, there was no significant difference in the 1-year cumulative incidence of NRM in the BEAM 5% (95%CI 3–6%) versus R-BEAM 6% (95%CI 3–10%) groups (p=0.44; Table 2; Figure 1A). On multivariate analysis (MVA), age; ≥65 years was associated with a higher NRM risk (HR: 6.72; 95%CI=1.63–27.78; p=0.01) (Table 3). The NRM risk was not significantly different between the BEAM and R-BEAM cohorts (HR: 1.43; 95%CI=0.91–2.26; p=0.12).

The 4-year cumulative incidence of relapse/progression was 44% (95%CI=40–48%) in the BEAM and 41% (95%CI=33–48%) in the R-BEAM cohort (p=0.40; Table 2, Figure 1B). On MVA, R-BEAM did not significantly reduce the risk of relapse (HR: 0.83; 95%CI=0.65–1.07; p=0.15) (Table 3). Relative to patients in CR, patients in PR prior to transplant were at significantly higher risk of relapse/progression (HR1.81; 95%CI=1.47–2.23; p=<0.0001).

Progression-free and Overall Survival

The 4-year PFS was 47% (95%CI=43–51%) in the BEAM cohort compared to 48% (95%CI=41–56%) in the R-BEAM group (p=0.77; Table 2, Figure 1C). On MVA, R-BEAM regimen was not associated with a significantly improved PFS (HR=0.94; 95%CI=0.76–1.18; p=0.61). Variables independently predictive of PFS are shown in Table 3.

The 4-year OS was 61% (95%CI=57–65%) in the BEAM cohort compared to 58% (95%CI=51–65%) in the R-BEAM group (p=0.77; Table 2, Figure 1D). On MVA, R-BEAM did not reduce mortality risk relative to BEAM conditioning (HR=1.03; 95%CI=0.81–1.31; p=0.83). On MVA, irrespective of the conditioning approach, older age (≥50years), PR before auto-HCT and history of early chemoimmunotherapy failure were independently associated with higher mortality risk after auto-HCT (Table 3).

Impact of Rituximab Dose

In patients who received R-BEAM in conditioning, the median rituximab dose during conditioning was 375mg/m^2 (range: 375–2012 mg/m^2). One hundred and eight patients received a dose of 375mg/m^2; while 85 patients received a dose of >375mg/m^2; (dose missing N=2). During conditioning, the most common start date of rituximab was day −6 (n=38; 19.5%), followed by day −8 (n=34; 17.4%) and day +1 (n=29; 14.8%). We also evaluated the effect of rituximab dose intensity in conditioning (375 mg/m^2 vs >375 mg/m^2) on transplant outcomes and noted no difference in NRM, relapse/progression, PFS or OS (Table 4).

Causes of Death

The leading cause of death was disease relapse in both groups – 68% (n=179) in the BEAM versus 55% (n=48) in the R-BEAM cohort (Table 5). Infection was the primary cause of death in 15 (6%) BEAM cases and 6 (7%) R-BEAM cases. In addition, infection was a contributing (secondary) cause of death in 13 (5%) BEAM and 5 (6%) R-BEAM deaths.

Impact of Remission Status and Peri-transplant Rituximab Exposure

A higher proportion (albeit not statistically significant) of BEAM patients were in CR at auto-HCT compared to R-BEAM subjects (63% vs. 55%; p=0.07; Table 1). A subgroup analysis limited to patients in CR at auto-HCT did not show any significant differences between the BEAM and R-BEAM groups in terms of NRM, relapse/progression, PFS and OS (4-year OS 68% vs. 62%; p=0.27; for details see Supplemental Materials Table S3). In addition, a subgroup analysis limited to patients who did not receive rituximab either in the last line of therapy before HCT or during mobilization, also did not show any significant difference between BEAM and R-BEAM cohorts (Table S4).

Discussion

In this large CIBMTR analysis we evaluated the impact of adding rituximab to BEAM conditioning in DLBCL patients undergoing auto-HCT and make several important observations; R-BEAM conditioning (a) did not delay engraftment, or (b) increase the risk of early or fatal infections and that (c) there was no improvement in the relapse rate, NRM or survival compared to BEAM conditioning regimen.

In the contemporary era, the benefit of combining an anti CD20 monoclonal antibody with auto-HCT conditioning regimens is yet to be determined. Prospective data published to date incorporating rituximab with conditioning regimens are either non-randomized studies or lack a BEAM-only comparative arm. Although, the BMT CTN 0410 trial was a randomized study, the comparison was between 2 novel conditioning regimens R-BEAM and B-BEAM, with no comparative arm with standard conditioning regimens, thus not addressing our research question[7]. Also, BMT CTN 0410 results may have minimal clinical impact as radioimmunoconjugates are not widely used in practice due to several logistical barriers. A report by Flohr et al. suggested encouraging response rates with incorporation of rituximab in the conditioning regimen[6]. This study was done when the use of rituximab was not highly prevalent and the first exposure to an anti-CD20 monoclonal antibody likely resulted in the observed response rates in a predominantly rituximab-naïve patient population. Similarly, a few earlier studies that primarily enrolled immunotherapy naïve patients revealed improved outcomes with incorporation of monoclonal antibody with mobilization approaches or during post-transplant period, but these findings may not be relevant in the current era of rituximab[13–16].

In contrast to our study, a recent retrospective CIBMTR analysis demonstrated improved PFS in both aggressive and low-grade B cell NHL with addition of rituximab to reduc-intensity conditioning (R-RIC) regimens for allogeneic HCT[17]. The 3-year PFS was 56% in R-RIC versus 47% in non R-RIC group (p=0.005). However, this did not translate into better NRM or OS. Moreover, observations from the above mentioned analysis cannot be extrapolated to a clinically very different DLBCL patient population undergoing auto-HCT (as in our current analysis). Finding from our present registry analysis demonstrate that administration of rituximab with auto-HCT conditioning regimens may not yield significant benefit in the modern era, especially in patients with previous exposure to anti-CD20 monoclonal antibody. Given the long half-life of rituximab, we did a subgroup analysis of patients who did not receive rituximab during the last line of therapy or mobilization and

again observed no significant difference in the outcomes of the 2 conditioning regimens (BEAM vs. R-BEAM) (Table S4).

Consistent with previously published data, our analysis identified early chemoimmunotherapy failure as a poor prognostic factor for survival in both groups. In the CORAL (Collaborative Trial in Relapsed Aggressive Lymphoma) study evaluating the outcomes of 2 different pre-transplant salvage regimens, patients with early relapse (<12 months from initial diagnosis) experienced lower response rate (46% vs 88%; p=<0.001) and inferior 3-year EFS (20% vs 45%)[10]. This was further corroborated in the CIBMTR study that also demonstrated higher risk of relapse (relative risk 2.08; p=<0.001) and mortality post auto-HCT in DLBCL with early chemoimmunotherapy failure compared to late rituximab failure[11]. Additional multicenter and single institution retrospective studies have validated early rituximab-based regimen failure as a negative predictor for transplant outcomes[18–20].

Center practice varies in terms of rituximab dose intensity and administration schedule in auto-HCT conditioning. While it is plausible that higher rituximab doses intensity may improve auto-HCT outcomes, in our current analysis patients who received higher dose level of rituximab (>375 mg/m^2) had similar relapse rate, and survival compared to patients receiving the standard 375 mg/m^2 dose (Table 4). Variations in rituximab dose applied with BEAM conditioning in our analysis (although reflective of practice variations), is a limitation we acknowledge. While the date of start of rituximab administration relative to HCT conditioning is captured in registry, the full administration schedule is not available. As a known inherent limitation with most retrospective studies, our analysis could not adjust for unknown clinical factors that could have prompted a center to add (or not to add) rituximab to BEAM conditioning (e.g. center practice, remission status at auto-HCT, history of rituximab intolerance and/or resistance etc.).

Disease relapse remains the main challenge and the primary cause for mortality post auto-HCT in DLBCL. In our cohort, progressive disease was the major cause of death in 68% and 55% of patients in the BEAM and R-BEAM group respectively. Post transplant maintenance is another treatment modality of interest in the ongoing efforts to curtail post-HCT relapse. The CORAL study that randomized patients post auto-HCT to rituximab maintenance for 1-year versus observation failed to demonstrate improvement in the CR and relapse rate, EFS and OS with maintenance therapy[10]. Due to lack of evidence, the ASBMT (American Society for Blood and Marrow Transplantation), CIBMTR, and EBMT joint consensus statement does not endorse post auto-HCT maintenance treatment in patients with DLBCL[21]. Results from the ongoing BMT CTN phase III randomized trial will address if maintenance ibrutinib post auto-HCT can impact outcomes in non-germinal center DLBCL (ClinicalTrials.gov #NCT02443077).

In this large CIBMTR study, addition of rituximab to BEAM conditioning regimen did not improve auto-HCT relapse rate or survival outcomes in patients with DLBCL. There was no delay in hematopoietic recovery or increased risk of early infections post auto-HCT. In the modern-era, where rituximab is an integral part of DLBCL therapy, both in the upfront and relapsed setting, additional rituximab exposure with the conditioning chemotherapy does not

appear to impact transplant outcomes. Older age at transplantation and evidence of residual disease pre-transplant were associated with inferior PFS and OS. Failure of frontline chemoimmunotherapy within 1-year of diagnosis conferred higher risk of mortality. Based on our results, routine use of rituximab with BEAM conditioning prior to auto-HCT for DLBCL is not recommended.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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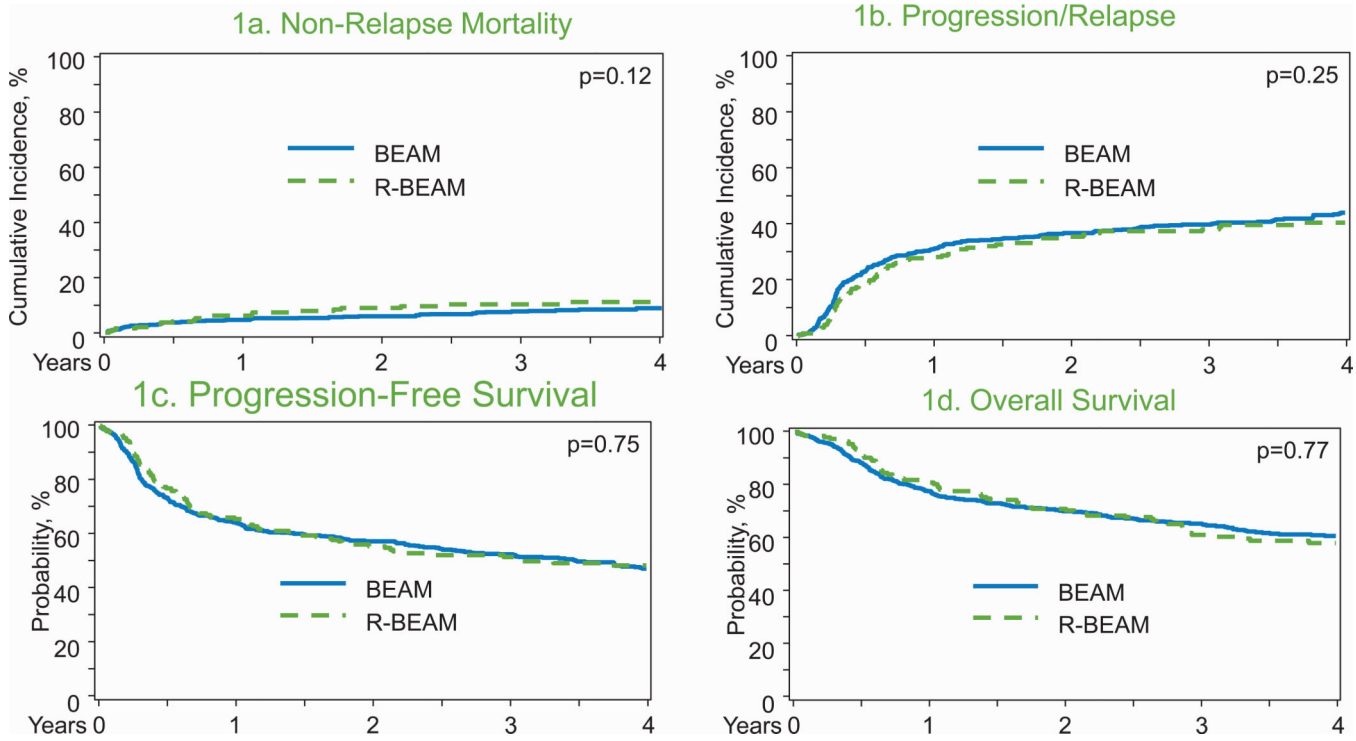

Figure 1:

Transplant outcomes in BEAM (carmustine, etoposide, cytarabine and melphalan) and R-BEAM (rituximab +BEAM) group. **(A)** Non relapse mortality in BEAM and R-BEAM cohort. **(B)** Progression/relapse in the BEAM and R-BEAM cohort. **(C)** Progression free survival in the BEAM and R-BEAM cohort. **(D)** Overall survival in the in the BEAM and R-BEAM cohort.

Table 1.

Baseline characteristics of patients receiving BEAM (with or without rituximab) conditioning regimen and autologous HCT for DLBCL during 2003–2017

	BEAM	R-BEAM	P Value
Number of patients	**667**	**195**	
Number of centers	93	35	
Median patient age, years (range)	61 (18–80)	60 (20–77)	0.83
≥ 65 years	218 (33)	60 (31)	
Male sex	393 (59)	115 (59)	0.99
Patient race[1]			0.38
Caucasian	520 (78)	159 (82)	
African American	82 (12)	22 (11)	
Asian	44 (7)	6 (3)	
Other	7 (1)	2 (1)	
Missing	14 (2)	6 (3)	
Karnofsky Performance Score ≥ 90	368 (55)	100 (51)	0.39
Missing	17 (3)	8 (4)	
Stage III-IV at diagnosis	155 (23)	44 (23)	0.65
Missing	61 (9)	14 (7)	
LDH elevated at diagnosis	89 (13)	27 (14)	0.98
Missing	398 (60)	115 (59)	
Median number of lines of therapy prior to HCT	2 (1–5)	2 (1–5)	0.26
1–2 lines	440 (66)	137 (70)	
3–5 lines	227 (34)	58 (30)	
No bone marrow involvement at diagnosis	474 (71)	149 (76)	0.26
Missing	57 (9)	11 (6)	
CNS involved at diagnosis	5 (<1)	3 (2)	0.59
Extranodal involvement at diagnosis	393 (59)	118 (61)	0.42
Missing	57 (9)	11 (6)	
Median Time from diagnosis to HCT (range)	17 (2–313)	17 (3–140)	0.32
Early chemoimmunotherapy failure[2]			0.48
No	313 (47)	84 (43)	
Yes	343 (51)	109 (56)	
Missing	11 (2)	2 (1)	

	BEAM	R-BEAM	P Value
Remission status			0.07
Complete remission	418 (63)	108 (55)	
Partial remission	249 (37)	87 (45)	
Primary refractory after first line of therapy			0.85
No	402 (60)	121 (62)	
Yes	236 (35)	67 (34)	
Missing	29 (4)	7 (4)	
Rituximab given with last therapy line prior to HCT and/or with mobilization	504 (76)	168 (86)	0.002
Median follow-up of survivors (range), months	48 (1–171)	64 (3–142)	

[1]Patient race -other: **BEAM**: 2 Pacific Islander; 5 Native American. **R-BEAM**: 2 Native American.

[2]Early therapy failure defined as not achieving CR after first line R+chemo, or relapse/progression within 1-year of DLBCL diagnosis.

Abbreviations: BEAM: - carmustine, etoposide, cytarabine and melphalan; R-BEAM: rituximab +BEAM; LDH: lactate dehydrogenase; HCT: hematopoietic cell transplantation; CNS: central nervous system; DLBCL: diffuse large B cell lymphoma

Table 2.

Univariate outcomes of patients receiving BEAM conditioning regimen and autologous HCT for DLBCL during 2003–2017

	BEAM (N = 667)		R-BEAM (N = 195)		
Outcomes	**N Eval**	**Prob (95% CI)**	**N Eval**	**Prob (95% CI)**	**p-value**
Neutrophil recovery	665		193		0.18
30-day		99 (98–100)%		98 (96–100)%	0.50
Platelet recovery	663		192		0.72
100-day		97 (96–98)%		97 (94–99)%	0.91
Non-relapse mortality	667		195		0.12
1-year		5 (3–6)%		6 (3–10)%	0.44
4-year		9 (7–11)%		11 (7–16)%	0.39
Relapse/progression	667		195		0.25
1-year		31 (28–35)%		28 (22–35)%	0.41
4-year		44 (40–48)%		41 (33–48)%	0.40
Progression-free survival	667		195		0.75
1-year		64 (60–68)%		65 (59–72)%	0.69
4-year		47 (43–51)%		48 (41–56)%	0.77
Overall survival	667		195		0.77
1-year		78 (74–81)%		81 (75–86)%	0.33
4-year		61 (57–65)%		58 (51–65)%	0.54

Abbreviations: BEAM: carmustine, etoposide, cytarabine and melphalan; R-BEAM: rituximab +BEAM; N Eval: number evaluated; Prob: probability; HCT: hematopoietic cell transplantation; DLBCL: diffuse large B cell lymphoma

Table 3.

Multivariate analysis

	N	HR	95% CI Lower Limit	95% CI Upper Limit	Overall p-value	p-value
Relapse						
Rituximab use in conditioning						
BEAM	667	1			0.15	
R-BEAM	195	0.83	0.65	1.07		0.15
Remission status						
Complete remission	526	1			<.0001	
Partial remission	336	1.81	1.47	2.23		<.0001
Non-relapse mortality (NRM)						
Rituximab use in conditioning						
BEAM	667	1			0.12	
R-BEAM	195	1.43	0.909	2.26		0.12
Age Group						
18–39	72	1			0.001	
40–49	113	2	0.40	9.92		0.40
50–59	229	3.25	0.76	13.89		0.11
60–64	170	3.98	0.92	17.16		0.06
≥65	278	6.72	1.63	27.78		0.01
Progress-free survival (PFS)						
Rituximab use in conditioning						
BEAM	667	1			0.61	
R-BEAM	195	0.94	0.76	1.18		0.61
Age Group						
18–39	72	1			0.0002	
40–49	113	1.42	0.87	2.30		0.16
50–59	229	1.6	1.04	2.49		0.03
60–64	170	1.70	1.09	2.65		0.02
≥65	278	2.26	1.48	3.45		0.0002
Remission status						
Complete remission	526	1			<.0001	
Partial remission	336	1.78	1.47	2.14		<.0001
Overall Survival (OS)						
Rituximab use in conditioning						
BEAM	667	1			0.83	
R-BEAM	195	1.03	0.81	1.31		0.83
Age Group						
18–39	72	1			<.0001	
40–49	113	1.30	0.71	2.38		0.40

	N	HR	95% CI Lower Limit	95% CI Upper Limit	Overall p-value	p-value
50–59	229	2.09	1.23	3.57		0.007
60–64	170	2.19	1.27	3.78		0.005
≥65	278	3.05	1.81	5.13		<.0001
Remission status						
Complete remission	526	1			<.0001	
Partial remission	336	1.67	1.39	2.07		<.0001
Early chemoimmunotherapy failure						
No	397	1			0.001	
Yes	452	1.52	1.22	1.91		0.0002
Missing	13	1.32	0.54	3.26		0.54

Abbreviations: BEAM: carmustine, etoposide, cytarabine and melphalan; R-BEAM: rituximab +BEAM; HR: hazard ratio; CI=: confidence interval; N: number of patients

Table 4.

Univariate analysis results of patients receiving BEAM conditioning regimen and autologous HCT for DLBCL during 2003–2017 by dose group

	375 mg/m^2 (N = 104)		> 375 mg/m^2 (N = 89)		
Outcomes	**N Eval**	**Prob (95% CI)**	**N Eval**	**Prob (95% CI)**	**p-value**
Non-relapse mortality	104		89		0.96
1-year		6 (2–11)%		6 (2–11)%	0.96
4-year		12 (6–19)%		9 (4–16)%	0.58
Progression/relapse	104		89		0.45
1-year		22 (15–31)%		35 (25–45)%	0.05
4-year		40 (30–51)%		42 (32–53)%	0.82
Progression-free survival	104		89		0.46
1-year		72 (63–80)%		59 (49–69)%	0.07
4-year		48 (37–59)%		49 (38–59)%	0.91
Overall survival	104		89		0.47
1-year		83 (76–90)%		80 (71–87)%	0.49
4-year		61 (50–71)%		57 (46–67)%	0.59

Abbreviations: BEAM: carmustine, etoposide, cytarabine and melphalan; R-BEAM: rituximab +BEAM; HR: hazard ratio; CI=: confidence interval; N: number of patients; N Eval: number evaluated; Prob: probability; auto-HCT: autologous hematopoietic cell transplantation; DLBCL: diffuse large B cell lymphoma

Table 5.

Causes of death of patients receiving BEAM conditioning regimen and autologous HCT for DLBCL during 2003–2017

	BEAM	R-BEAM
Number of patients	265	87
Primary disease	179 (68)	48 (55)
Organ failure	19 (7)	4 (5)
Infection	15 (6)	6 (7)
Second malignancy	12 (5)	13 (15)
Idiopathic pneumonia syndrome/Acute respiratory distress syndrome	5 (2)	1 (1)
Hemorrhage	4 (2)	1 (1)
Graft-versus-host disease[1]	3 (1)	1 (1)
Vascular	1 (<1)	1 (1)
Other[2]	2 (<1)	2 (2)
Missing	25 (9)	10 (11)

[1] 4 cases had subsequent allogeneic transplantation.

[2] Other cause: **BEAM**: 1 progressive multifocal encephalopathy; 1 sudden death. **R-BEAM**: 2 accidental death.

[3] Infection as secondary cause of death: **BEAM**: 13 (5); **R-BEAM:** 5 (6).

Abbreviations: BEAM: carmustine, etoposide, cytarabine and melphalan; R-BEAM: rituximab +BEAM; auto-HCT: autologous hematopoietic cell transplantation; DLBCL: diffuse large B cell lymphoma