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Comparison of Fludarabine Versus Bendamustine as a Lymphodepleting Chemotherapy Prior to CAR-T for Large Cell Lymphoma

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Lymphodepleting chemotherapy (LD) enhances chimeric antigen receptor T cell (CAR-T) expansion, persistence, and clinical activity. Fludarabine-cyclophosphamide is most used, but the benefit of alternative agents is unknown. This study compares fludarabine- versus bendamustine-based LD in the real-world setting prior to CAR-T treatment of relapsed or refractory large cell lymphoma (LBCL). We assessed outcomes of patients with LBCL who received commercial CD19 CAR-T therapies during 2017 to 2023, using data from Center for International Blood and Marrow Transplant Research. Of 5256 patients with LBCL treated with axicabtagene ciloleucel, tisagenlecleucel, or lisocabtagene maraleucel, 92% and 9% received fludarabine and bendamustine LD, respectively. Multivariate analyses showed bendamustine had inferior overall response rate (ORR) (hazard ratio [HR] 0.773, $P = .0013$), but there was no difference in complete response (HR 0.828, $P = .0606$). The 1-year and 2-year rates of progression-free survival (PFS) were lower for bendamustine ($P = .04$), and the 1-year and 2-year rates of overall survival (OS) were similar ($P = .65$) The bendamustine group had lower rates of toxicities than the fludarabine group, including severe cytokine release syndrome (odds ratio [OR] 0.445, $P < .0001$), immune effector cell-associated neurotoxicity syndrome (OR 0.432, $P < .0001$), prolonged cytopenia (OR 0.479, $P < .0001$) Treatment-related mortality (TRM) was lower in the bendamustine group. In a subset analysis adjusting for distribution of LD regimens, the main conclusions were the same. Regardless of CAR-T products used, compared to patients who received bendamustine, patients who received fludarabine LD had higher ORR and PFS, without significant impact on OS. Bendamustine was associated with a reduced incidence of toxicities and TRM. Providers can consider relevant patient characteristics when choosing LD and the trade-off between efficacy and safety. Bendamustine can be considered an alternative LD prior to CAR-T for LBCL.

INTRODUCTION

Anti-CD 19 chimeric antigen receptor T cell (CAR-T) therapies, including axicabtagene autoleucel (axi-cel), tisagenlecleucel (tisa-cel), and lisocabtagene maraleucel (liso-cel) are standard therapies in relapsed or refractory large B-cell lymphoma (LBCL). CAR-T cell kinetics, including peak expansion and effector function, are key

determinants of response [1,2]. Lymphodepleting (LD) chemotherapy improve CAR-T cells efficacy, in part by inducing a favorable cytokine milieu that supports CAR-T cells expansion and persistence, and is a fundamental component of CAR-T and other T-cell adoptive therapies [3,4]. Fludarabine-based LD has been the mainstay LD regimen, and the most widely used LD regimen remains fludarabine plus cyclophosphamide (Flu/Cy), at doses of 25 to 30 mg/m^2 Flu and 250 to 500 mg/m^2 Cy, for 3 days. The primary toxicity associated with this regimen is hematologic toxicity [5,6].

Studies have explored CAR-T efficacy using various LD agents and dosing schedules beyond Flu/Cy, including bendamustine, interleukin-2, total body irradiation, and pentostatin, with varying degrees of success [7]. Bendamustine (90 mg/m^2 for 2 days) is the most promising alternative, because of its antilymphoma activity, potent lymphodepleting effect, and good tolerability. A bendamustine-based LD regimen was used in JULIET and was studied in a CD30 CAR-T trial for Hodgkin lymphoma [8–11]. In the JULIET trial, 19% of patients received bendamustine; long-term follow-up suggests that compared to the bendamustine group, the Flu/Cy group had improved progression-free survival (PFS) [9]. The fludarabine supply shortage in 2022 prompted CAR-T treatment centers to explore alternate LD regimens for these time-sensitive therapies [11,12]. Bendamustine was the most used regimen during that period. Despite this, there are limited data on the impact of different LD regimens [1–4].

This study evaluates the outcomes of fludarabine-based vs bendamustine-based LD prior to CD19-targeted CAR-T for the treatment of LBCL in the real world.

METHODS

Data Source and Ethics

Center for International Blood and Marrow Transplant Research (CIBMTR) is a research collaboration between the Medical College of Wisconsin and NMDP. More than 320 medical centers worldwide submit clinical data about transplant and cellular therapies to CIBMTR; CIBMTR's Research Database includes long-term clinical data from more than 750,000 patients, including more than 35,600 CAR-T recipients [13–17].

CIBMTR protects the privacy of participants and obeys international laws and ethical guidelines regarding human rights. The NMDP Institutional Review Board reviews CIBMTR's research. Patients or guardians give informed consent for research.

CIBMTR performs automated and manual quality checks of data and conducts on-site audits. These validations and verifications produce high-quality data. If a center fails to meet data-quality standards, then its data are removed from research studies.

Patients and Study Design

This observational, multicenter study used CIBMTR data to assess the outcomes of patients with diffuse, large B-cell lymphoma (DLBCL) who received commercial, standard-of-care infusions of axi-cel, tisa-cel, and liso-cel, with either fludarabine-based or bendamustine-based LD. Adults with DLBCL who received their first CD19 CAR-T infusion during 2017 to 2023 in the US with at least 3 months of follow-up were included. Patients were excluded if they were treated outside the US, enrolled in clinical trials, or received LD other than fludarabine or bendamustine (Figure S1).

Patients were stratified according to fludarabine or bendamustine LD to compare these 2 regimens and their effects on outcomes. Patients who received CAR-T infusion during 2021 to 2023 were included in the subset analysis based on the year of infusion, because this is the period when bendamustine use increased because of a fludarabine shortage. Additionally, certain baseline labs, including serum creatinine, lactate dehydrogenase (LDH), ferritin, and C-reactive protein (CRP), were not captured in the database prior to 2021, so they were only described for this subgroup.

Objectives and Definitions

The primary objective was to determine the impact of LD on overall response rates (ORR) at Day 100 and Day 180. ORR was defined as complete response (CR) or partial response (PR) at the time points of interest. Secondary endpoints included PFS, overall survival (OS), and treatment-related toxicities. We assessed the incidence and severity of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) per the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading system [18]. We also analyzed prolonged cytopenia and causes of death by Day 30 and Day 100.

Prolonged cytopenia was defined as the lack of neutrophil engraftment (absolute neutrophil count [ANC] $<500/mm^3$) and/or platelet recovery (platelet count $<20 \times 10^9$/L) through Day 30 after infusion. Persistent cytopenia was evaluated at Day 100 and Day 180 using criteria from Common Terminology Criteria for Adverse Events version 5 (CTCAE) [19]. Grade 3 to 4 neutropenia at Day 100

and at Day 180 after infusion was described according to CTCAE criteria19: ANC 500 to 1000/mm^3 (grade 3) and ANC $< 500/mm^3$ (grade 4). At Day 100 and at Day 180, we graded thrombocytopenia according to CTCAE criteria:19 grade 3 was defined as platelets 25 to $<50 \times 10^9$/L, and grade 4 was defined as platelets $<25 \times 10^9$/L. To ensure accurate assessment of prolonged cytopenia, only surviving patients without disease progression were evaluated for this outcome.

Statistical Methods

We used descriptive statistics to summarize the data. Patient-, disease-, and CAR-T-related factors were compared between groups using the chi-square test for categorical variables and the Wilcoxon 2-sample test for continuous variables. For univariate analysis, the probability of OS and PFS for the bendamustine and fludarabine LD groups was calculated using the Kaplan–Meier estimator, with the variance estimated by Greenwood's formula. Cumulative incidence estimates were calculated for competing-risks outcomes, including response outcomes, with deaths before responses as a competing risk event.

A multivariable model of the main cohort of patients who received commercial CD19 CAR-T cell therapy with fludarabine or bendamustine LD was conducted to identify significant factors associated with CAR-T outcomes. Factors considered in model-building were age at CAR-T, race, ethnicity, Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI), Karnofsky Performance Status (KPS) prior to CAR-T, Eastern Cooperative Oncology Group (ECOG) performance status, LDH before infusion, disease status at last evaluation prior to CAR-T, CAR-T product, and bridging therapy. A Cox proportional hazards model was fitted for PFS and OS. The proportional hazard assumption was checked. If violated, variables were included as time-dependent. For competing-risks outcomes, including ORR and CR, the cause-specific hazard model was used. Logistic regression models were fitted for any grade CRS, any grade ICANS, and prolonged cytopenia. A stepwise variable selection approach was used, and variables that attained a P value less than 1% were retained in the final model. The interactions between main effects and other significant variables were tested. Center effects were tested using the score test. Subset analyses for patients who received CD19 CAR-T cell therapy during the years 2021 to 2023 were performed to account for the period of interest during the fludarabine shortage. In addition to the variables listed above, year of CAR-T, baseline hemoglobin, and baseline platelet count were also tested.

RESULTS

Patient Demographics and Baseline Characteristics

Of 5256 patients, 4809 (92%) received fludarabine LD and 447 (8%) received bendamustine LD (Table 1). The majority (99%) of the fludarabine group received Flu/Cy, while the majority of the bendamustine group received bendamustine alone (100%). The median total dose of fludarabine was 90 mg/m^2 for axi-cel, and 75 mg/m^2 for tisa-cel and liso-cel. The median total dose of cyclophosphamide was 1500 mg/m^2 for ax-cel and 750 mg/m^2 for tisa-cel and liso-cel. The median total bendamustine dose was 180 mg/m^2 for each product (Table 1). Of the whole cohort, 3599 (68%) received axi-cel, 1220 (23%) tisa-cel, and 437 (8%) received liso-cel. The highest proportion of patients who received bendamustine LD were tisa-cel recipients (14%), followed by liso-cel (11%) and axi-cel (6%). The median age was 64.4 years (18 to 91.2). Black or African American patients comprised 5% of the fludarabine group and 6% of the bendamustine group. About 55% of all patients received bridging therapy, which was similar between the LD groups.

Key differences were observed between the LD groups. Compared to the fludarabine-based group, a greater proportion of patients in the bendamustine-based group had KPS < 80 (20% versus 26%; $P < .01$). LDH prior to LD was higher in the bendamustine group than the fludarabine group (34% versus 21%, $P < .01$). Most patients (64%) had refractory disease at the time of CAR-T, though this was less frequent in the bendamustine group (56% versus 65%, $P < .01$). Patients in the bendamustine group had fewer lines of therapy, with ≥ 3 prior lines being 51% in the bendamustine group versus 62% in the fludarabine group, ($P < .01$). Additionally, the interval from leukapheresis to infusion was longer in the bendamustine group (35 days versus 32 days, $P < .01$).

The subset analysis included 2935 (56%) patients who received CAR-T infusions during 2021 to 2023, of whom 2571 patients (88%) and 364 (12%) received fludarabine and bendamustine LD, respectively (Table S1). Of this subset, 64% received tisa-cel, 22% axi-cel, and 15% received liso-cel; and there was a more even distribution

Table 1
Baseline Characteristics of Patients With DLBCL

Characteristic	Fludarabine	Bendamustine	Total	*P* Value
No. of patients	4809	447	5256	
Age, median (range), yr	64.3 (18.0-91.2)	65.3 (20.4-86.3)	64.4 (18.0-91.2)	.08
Age, no. (%)				.19
≤65 yr	2512 (52.2)	219 (49.0)	2731 (52.0)	
65 yr	2297 (47.8)	228 (51.0)	2525 (48.0)	
Male, no. (%)	3047 (63.4)	277 (62)	3324 (63.2)	0.8
Ethnicity, no. (%)				<**.01**
Hispanic or Latino	488 (10.1)	47 (10.5)	535 (10.2)	
Not Hispanic or Latino	3718 (77.3)	368 (82.3)	4086 (77.7)	
Unknown or not applicable	603(12.6)	32 (7.2)	635 (12.1)	
Race, no. (%)				<**.01**
White	3704 (77)	347 (77.6)	4051 (77.1)	
Black or African American	230 (4.8)	26 (5.8)	256 (4.9)	
Other/unknown	875 (18.2)	74 (16.6)	949((18)	
HCT-CI, no. (%)				.28
0	1443 (30.0)	121 (27.1)	1564 (29.8)	
1	935 (19.4)	100 (22.4)	1035 (19.7)	
2	645 (13.4)	67 (15.0)	712 (13.5)	
≥3	1724 (35.8)	156 (34.9)	1880 (35.8)	
Not reported	62 (1.3)	3 (0.7)	65 (1.2)	
KPS before infusion, no. (%)				<**.01**
90-100	1917 (39.9)	141 (31.5)	2058 (39.2)	
80	1484 (30.9)	140 (31.3)	1624 (30.9)	
<80	958 (19.9)	117 (26.2)	1075 (20.5)	
Not reported	450 (9.4)	49 (11.0)	499 (9.5)	
Disease classification, no. (%)				.07
DLBCL-GCB	1724 (35.8)	146 (32.7)	1870 (35.6)	
DLBCL-ABC	1289 (26.8)	119 (26.6)	1408 (26.8)	
DLBCL	1086 (22.6)	111 (24.8)	1197 (22.8)	
HGBL with *MYC* and *BCL2* and/or *BCL6* rearrangements	519 (10.8)	47 (10.5)	566 (10.8)	
PCNSL	22 (0.5)	4 (0.9)	26 (0.5)	
High-grade B-cell lymphoma NOS	103 (2.1)	13 (2.9)	116 (2.2)	
EBV-positive DLBCL NOS	50 (1.0)	5 (1.1)	55 (1.0)	
Primary cutaneous DLBCL leg type	14 (0.3)	1 (0.2)	15 (0.3)	
DLBCL associated with chronic inflammation	2 (0.0)	0 (0.0)	2 (0.0)	
HHV8+ DLBCL NOS	0 (0.0)	1 (0.2)	1 (0.0)	
Disease status at infusion, no. (%)				<**.01**
CR	233 (4.8)	46 (10.3)	279 (5.3)	
PR	487 (10.1)	61 (13.6)	548 (10.4)	
Refractory	3124 (65.0)	248 (55.5)	3372 (64.2)	
Prior lines of therapies, no. (%)				<**.01**
1	202 (4.2)	38 (8.5)	240 (4.6)	
2	1345 (28.0)	151 (33.8)	1496 (28.5)	
≥3	3026 (62.9)	228 (51.0)	3254 (61.9)	
Product, no. (%)				<**.01**
Axicabtagene ciloleucel	3366 (70.0)	233 (52.1)	3599 (68.5)	
Tisagenlecleucel	1053 (21.9)	167 (37.4)	1220 (23.2)	

(*continued*)

Table 1 (*Continued*)

Characteristic	Fludarabine	Bendamustine	Total	*P* Value
Lisocabtagene maraleucel	390 (8.1)	47 (10.5)	437 (8.3)	
Bendamustine doses, median (range) mg/m^2				
Axi-cel, bendamustine total dose	NE	180.0 (90-370)	180.0 (90-370)	
Tisa-cel, bendamustine total dose	NE	180.0 (70-472)	180.0 (70-472)	
Liso-cel, bendamustine total dose	NE	180.0 (70-472)	180.0 (70-472)	
Fludarabine and cyclophosphamide doses, median (range) mg/m^2				
Axi-cel, fludarabine total dose	90.0 (22.5-3240)	NE	90.0 (22.5-3240)	
Axi-cel, cyclophosphamide total dose	1500.0 (90-15,000)	NE	1500.0 (90-15,000)	
Tisa-cel, fludarabine total dose	75.0 (15-750)	NE	75.0 (15-750)	
Tisa-cel, cyclophosphamide total dose	750.0 (75-2280)	NE	750.0 (75-2280)	
Liso-cel, fludarabine total dose	75.0 (15-750)	NE	75.0 (15-750)	
Liso-cel, cyclophosphamide total dose	750.0 (75-2280)	NE	750.0 (75-2280)	
Bridging therapy, no. (%)	2629 (54.7)	254 (56.8)	2883 (54.9)	
Year of infusion				**<.01**
2017-2020	2238 (46.5)	83 (18.5)	2321 (44.2)	
2021-2023	2571 (53.5)	364 (81.4)	2935 (55.8)	
Follow-up of survivors, median (range), mo	23.8 (0.5-66.9)	9.8 (1.0-51.1)	22.9 (0.5-66.9)	

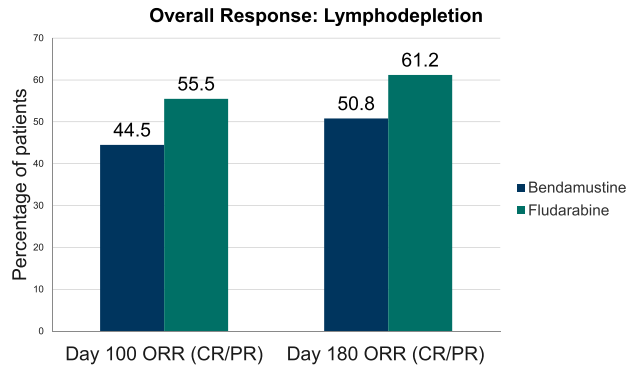
ABC indicates activated B-cell subtype; EBV-positive, Epstein-Barr virus-positive; GCB, germinal center B-cell subtype; HGBL, high-grade B-cell lymphoma; HHV8+, human herpesvirus 8-positive; NOS, not otherwise specified; PCNSL, primary central nervous system lymphoma. Significant *p* values appear in bold.

of LD regimen by product (Table S1, Figures S1, S2). The baseline characteristics of this group were overall similar to those of the whole cohort. Additional variables were more complete in the subset, including pre-LD cytopenia, creatinine clearance, ferritin, and CRP (Table S1).

Baseline neutropenia and thrombocytopenia at infusion were more frequent in the fludarabine group: (ANC < 1000 in 7% of fludarabine group versus 5% in bendamustine group, and platelet count <75,000 × 10^6/L in 10% versus 6%, respectively. Conversely, impaired renal function was more common in the bendamustine group, with 6% having a creatinine clearance <50 mL/min (6% bendamustine versus 2% fludarabine, $P < .01$).

Overall and Complete Response Rates

The median follow-up was 22.9 (0.5 to 66.9) months (fludarabine 24 months versus bendamustine 10 months, respectively). By 100 days, 63% of all patients achieved a best response of CR/PR (ORR) and 64% by Day 180. Compared to the bendamustine group, ORR was higher in the fludarabine group (ORR at Day 100: 51% for bendamustine versus 64% fludarabine; Day 180: 53% for bendamustine versus 65% for fludarabine; Figure 1). Similarly, CR was higher in the



Abbreviations: CR, complete remission; PR, partial remission; ORR, overall response rate

Figure 1. Overall response rate by lymphodepletion.

Table 2
Outcomes, by Fludarabine Versus Bendamustine Lymphodepletion

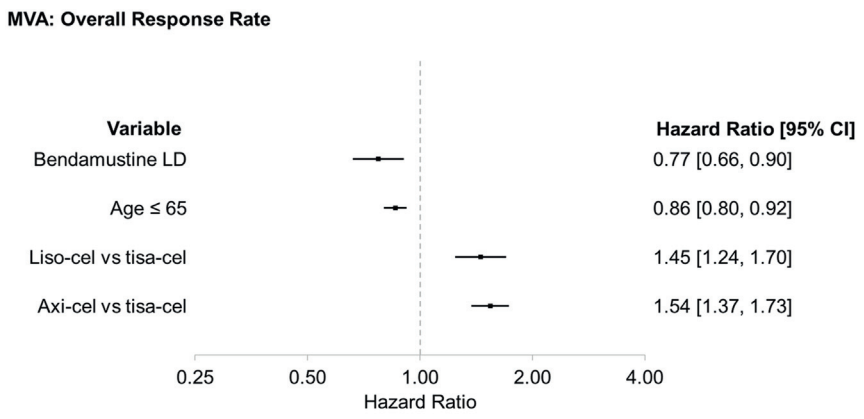
Outcome	Fludarabine No. (%)	Bendamustine No. (%)	*P* Value
Overall response rate			
100-d ORR	3078 (64.1)	230 (51.4)	<.01
180-d ORR	3130 (65.1)	238 (53.3)	<.01
Complete response			
100-d CR	2182 (45.4)	166 (37.1)	<.01
180-d CR	2348 (48.8)	176 (39.4)	<.01
Cytokine release syndrome			
Overall CRS	3723 (77.3)	273 (61.1)	<.01
Grade ≥3 CRS	368 (7.7)	20 (4.5)	.01
ICANS			
Overall ICANS	2124 (44.2)	103 (23)	<.01
Grade ≥3 ICANS	802 (16.7)	37 (8.3)	<.01
Prolonged cytopenia			<.01
Yes	987 (20.5)	52 (11.6)	
Death before Day 30	146 (3.0)	11 (2.5)	
Not reported	30 (0.6)	2 (0.4)	
Progression-free survival, censoring at subsequent HCT (95% CI)			.04
6-mo	54.5 (53.1-56.0)	51.3 (46.5-56.1)	
1-yr	45.4 (43.9-46.9)	39.1 (33.8-44.5)	
2-yr	37.6 (36.0-39.2)	35.7 (29.9-41.6)	
Relapse, censoring at subsequent HCT (95% CI)			<.01
6-mo	42.9 (41.5-44.4)	47.1 (42.3-52.0)	
1-yr	50.8 (49.2-52.3)	59.2 (53.7-64.6)	
2-yr	54.7 (53.1-56.3)	61.2 (55.2-67.0)	
Overall survival (95% CI)			.65
6-mo	76.2 (75.0-77.4)	77.9 (73.8-81.7)	
1-yr	62.2 (60.8-63.7)	61.0 (55.4-66.4)	
2-yr	48.0 (46.3-49.6)	50.2 (43.1-57.2)	
Treatment-related mortality (95% CI)			.04
3-mo	2.7 (2.2-3.3)	2.5 (1.1-4.4)	
6-mo	4.5 (3.8-5.2)	2.9 (1.4-5.0)	
1-yr	7.8 (6.8-8.9)	4.1 (1.7-7.6)	
2-yr	16.9 (15.1-18.9)	8.1 (3.0-15.4)	

fludarabine versus bendamustine group (Table 2). The cumulative incidence of overall response was also higher in the fludarabine group than the bendamustine group (Day 100: 56% versus 47%, $P < .01$; Day 180: 71% versus 61%, $P < .01$).

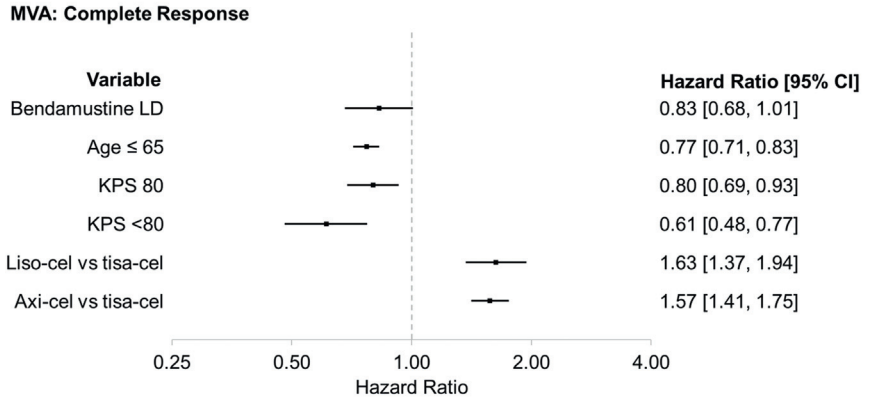
A multivariate analysis showed an inferior ORR in the bendamustine group than the fludarabine group (HR, 0.77; $P = .001$) and no significant difference in CR (HR 0.83, $P = .061$) (Table S2). Age 65 and younger was associated with inferior ORR and CR (ORR: HR, 0.86; $P < .001$; CR: HR, 0.77, $P < .001$). The CAR-T product also impacted the ORR, with both axi-cel (HR, 1.5, 95% CI, 1.4 to 1.7) and liso-cel (HR, 1.5; 95% CI, 1.2 to 1.7) associated with a higher ORR and were significantly higher than tisa-cel. There was no significant interaction between the LD regimen and the CAR-T product. The center effects for ORR and CR were significant and adjusted (Table S2, Figure 2). A subset analysis yielded similar results to the main cohort but with the addition that elevated LDH before infusion is associated with lower CR.

Toxicities and Associations With LD

Figure 3 summarizes the incidence of overall and severe CRS, ICANS, and prolonged cytopenia. Fludarabine LD was associated with higher rates of both CRS and ICANS than bendamustine (CRS, any grade: 77% versus 61%; and severe: 8% versus

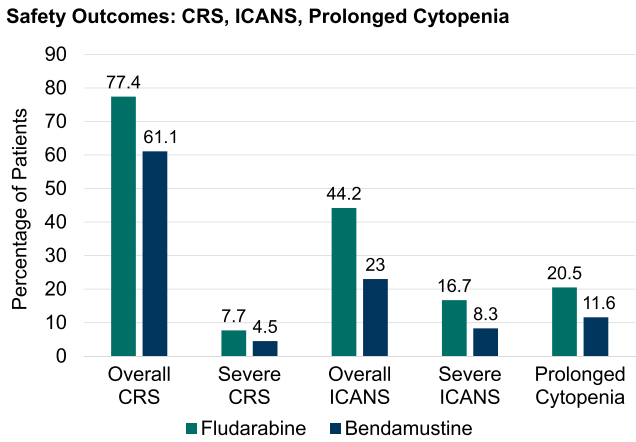


Abbreviations: axi-cel, axicabtagene ciloleucel; LD, lymphodepletion; liso-cel, lisocabtagene maraleucel; MVA, multivariable analysis; tisa-cel, tisagenlecleucel.



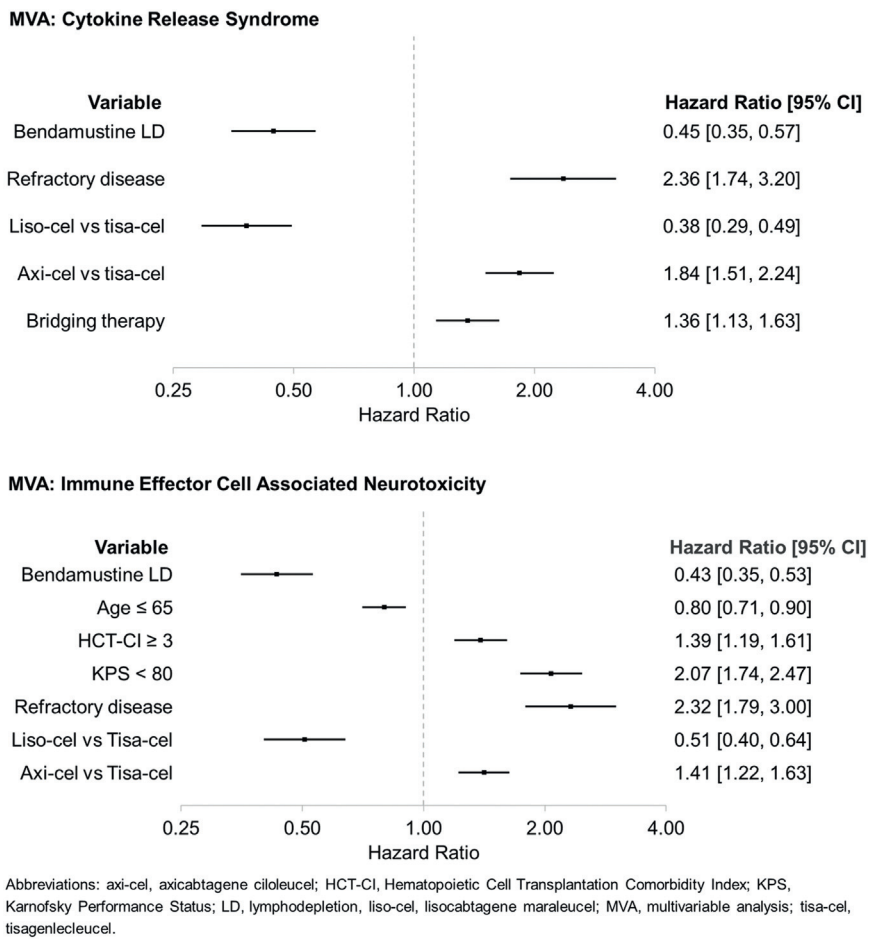
Abbreviations: axi-cel, axicabtagene ciloleucel; KPS, Karnofsky Performance Status; LD, lymphodepletion; liso-cel, lisocabtagene maraleucel; MVA, multivariable analysis; tisa-cel, tisagenlecleucel.

Figure 2. Overall response rate and complete response, multivariate analysis.



Abbreviations: CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity

Figure 3. Rates of cytokine release syndrome, ICANS, and prolonged cytopenia.



Abbreviations: axi-cel, axicabtagene ciloleucel; HCT-CI, Hematopoietic Cell Transplantation Comorbidity Index; KPS, Karnofsky Performance Status; LD, lymphodepletion, liso-cel, lisocabtagene maraleucel; MVA, multivariable analysis; tisa-cel, tisagenlecleucel.

Figure 4. Cytokine release syndrome and ICANS, multivariate analysis.

4%; P = .01) (ICANS any grade: 44% versus 23%; and severe: 17% versus 8%; P < .01).

Additionally, the fludarabine group had a higher incidence of prolonged cytopenia than the bendamustine group (20% versus 12%, P < .01). Neutropenia grade ≥3 was higher with fludarabine than bendamustine at Day 100 (15% versus 7%, P < .01) and at Day 180 (12% versus 4%, P < .01). Grade ≥3 thrombocytopenia was higher with fludarabine than bendamustine (at Day 100: 11% versus 3%, P < .01) (at Day 180: 7% versus 2%, P < .01).

The multivariate analysis indicated that bendamustine LD was associated with lower odds of CRS (OR, 0.45; P < .001), ICANS (OR, 0.43; P < .001), and prolonged cytopenia (OR, 0.48; P < .001) than fludarabine LD (Table S2).

Other Factors Influencing Toxicities

Disease status, particularly refractory disease (OR, 2.36; P < .001), prior to CAR-T infusion and use of bridging therapy (OR, 1.26; P < .001) were associated with higher overall CRS as well as ICANS (disease status of relapse: OR, 2.46; P < .001; refractory: OR, 2.32; P < .001), use of bridging therapy (OR, 1.54; P < .001; Table S2).

CAR-T product type also influenced toxicity outcomes. Axi-cel was associated with higher incidences of CRS than other products (OR, 1.84; P < .001), ICANS (OR, 1.41; P < .001), and prolonged cytopenia (OR, 1.3; 95% CI, 1.1 to 1.5; P < .001, (Table S2, Figures 4, S3). In contrast, liso-cel was associated with lower CRS, ICANS, and prolonged cytopenia than axi-cel and tisa-cel were (CRS: OR, 0.38; P < .001; ICANS: OR, 0.51; P < .001; prolonged cytopenia: OR, 0.52; P = .002). Other factors associated with increased risk of prolonged cytopenia included KPS < 80 (OR, 2.01; 95% CI, 1.6 to 2.4; P < .001) and use of bridging therapy (OR, 1.9; 95% CI, 1.7 to 2.3; P < .001) (Table S2, Figure S3).

Toxicities in the Subset Analysis

The subset analysis of patients treated during 2021 to 2023 (Table S3) yielded similar results to

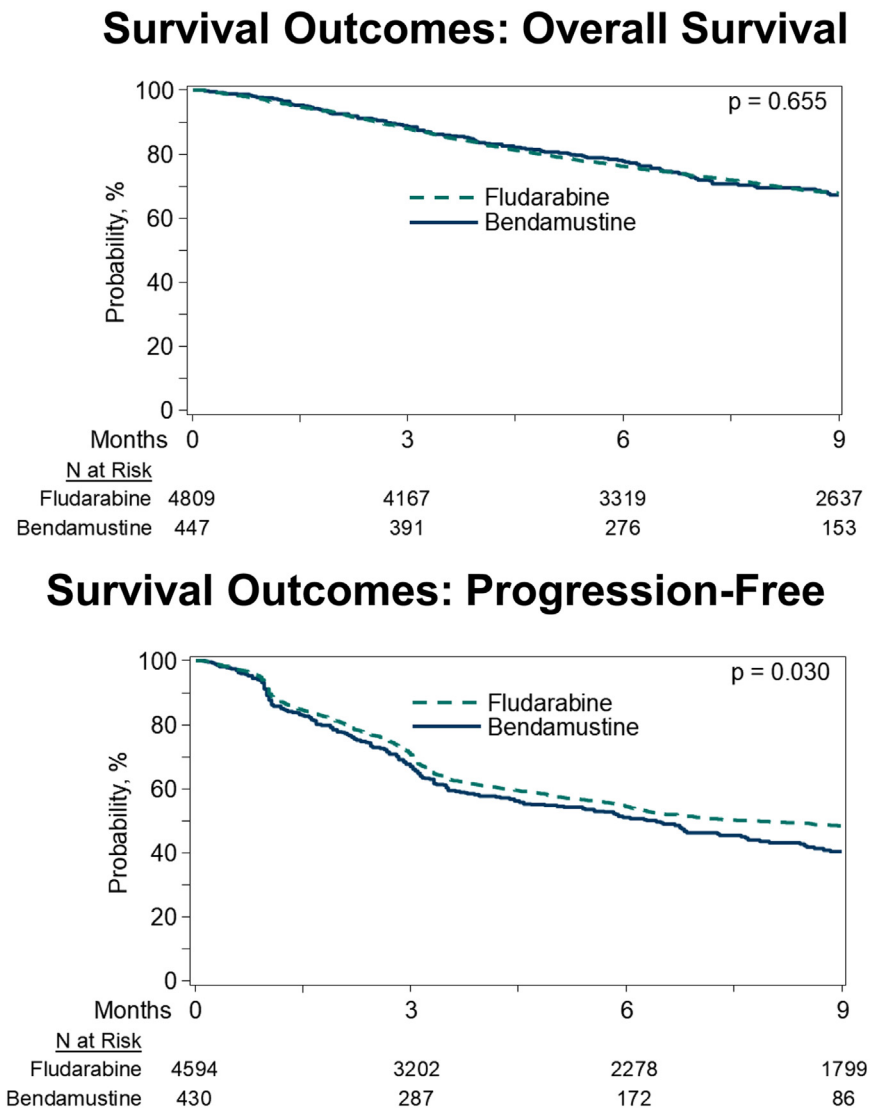


Figure 5. Overall survival and progression-free survival.

the main cohort. Elevated LDH (OR, 2.50; $P < .001$) and axi-cel (OR, 1.46; $P = .007$) were also associated with higher CRS. In addition to older age, bridging therapy, and CAR-T product, the subset analysis also found worse KPS (<80, OR, 1.992; $P < .001$), pre-LD anemia (hemoglobin <8) (OR, 2.37, $P < .001$), and pre-LD thrombocytopenia (<75,000) (OR, 1.68; $P = 001$) to be associated with higher ICANS. Pre-LD thrombocytopenia was also associated with worse prolonged cytopenia (OR, 5.09; $P < .001$). Liso-cel was again associated with lower CRS (OR, 0.38; $P < .001$), ICANS (OR, 0.62; $P < .001$), and prolonged cytopenia (OR, 0.53; $P = .001$) (Table S3).

Progression-free Survival, Relapse, and Overall Survival

For all patients, the 6-month PFS was 54% (95% CI, 52.8 to 55.6), and 6-month OS was 76.4 (95% CI, 75.2 to 77.5). The 6-month, 1-year, and 2-year PFS were 54%, 45%, and 38% for fludarabine and 51%, 39%, and 36% for bendamustine ($P = .04$) (Table 2, Figure 5). Relapse rates were lower for fludarabine compared to bendamustine at 6 months, 1 year, and 2 years (27%, 42%, and 54% for fludarabine and 31%, 47%, and 61% for bendamustine, respectively, $P < .01$) (Table 2). There were no significant differences were observed in OS at 6 months, 1 year, or 2 years (76%, 62%, and 48% for fludarabine, and 78%, 61%, and 50% for bendamustine, respectively, $P = .65$) (Table 2, Figure 5).

Factors Associated With Survival

In the multivariate analysis, LD regimen did not have significant impact on either OS ($P = .42$) or PFS ($P = .50$) (Table S2, Figures S4, S5).

In the multivariate analysis, factors associated with notably worse PFS and OS ($P < .001$)

included HCT-CI, KPS, refractory disease, and the use of bridging therapy (HCT-CI $\geq$ 3: PFS, HR, 1.51; OS, HR, 1.28); (KPS $<$ 80: PFS, HR, 1.59; OS, HR, 1.94); (refractory disease: PFS, HR, 1.88; OS, HR, 1.98) (bridging therapy: PFS, HR, 1.41; OS, HR, 1.48)

CAR-T product type also influenced survival outcomes. Compared to tisa-cel, axi-cel and liso-cel were associated with improved OS (HR, 0.8; 95% CI, 0.7 to 0.9; $P < .001$, and HR, 0.79; 95% CI 0.6 to 0.99; $P = .03$ respectively) and improved PFS (HR, 0.7; 95% CI, 0.6 to 0.8; $P < .001$; and HR, 0.70; 95% CI, 0.6 to 0.8; $P < .001$) (Table S2). There was no significant interaction between LD regimen and the CAR-T product on survival outcomes. There were significant center effects for OS and PFS, which were adjusted in the final model.

Treatment-related Mortality

We analyzed treatment-related mortality (TRM) based on LD regimens. The TRM in the fludarabine group was 3%, 5%, 8%, and 17% at 3 months, 6 months, 1 years, and 2 years respectively, compared to 3%, 3%, 4%, and 8% with bendamustine ($P = .04$).

Causes of Death

A total of 2395 patients (45%) died. The primary cause of death was disease progression in 68% (n = 1641), without a significant difference between LD regimen (fludarabine: 68%, bendamustine: 77%, $P = .06$). Other causes of death included infection in 11% (n = 267), organ failure in 6% (n = 148), neurotoxicity in 1% (n = 29), and CRS in 1% (n = 22) of patients (Figure S6).

DISCUSSION

Key Results

This study represents the largest comparative analysis of bendamustine-based LD and the more commonly used fludarabine-based LD regimen in patients who underwent CD19 CAR-T cell therapy for LBCL. We found that fludarabine-based LD was associated with a higher ORR than bendamustine-based LD, while PFS and OS were similar across both regimens, supporting bendamustine as a viable alternative LD regimen, particularly when fludarabine is unavailable. However, the shorter median follow-up in the bendamustine group (10 months versus 2 years for fludarabine LD) limits long-term survival interpretation, and the data on PFS and OS should be considered preliminary.

A key finding of this study was the more favorable toxicity profile associated with bendamustine-based LD, including significantly lower rates of CRS, ICANS, and prolonged cytopenia, consistent with previous reports [6,8–10,20–26]. These safety advantages may be attributed to bendamustine's effects on redox balance and its ability to suppress the production of pro-inflammatory cytokines (IL-15, IL-8, GM-CSF, IL-6, and IL-1β), which are key mediators of CAR-T-related toxicities [8,22,23]. This translated to an improved TRM with bendamustine. There is, however, a higher incidence of relapse. This translates to a lower PFS for the bendamustine group, even though there is no significant difference in OS. In addition to the favorable TRM for bendamustine, OS may be similar because of less cytopenia with bendamustine, which may allow the patients to receive subsequent effective therapies. Further analyses of effectiveness demonstrated that the ORR with bendamustine LD was consistent across all CAR-T products. However, patients receiving bendamustine-based LD had less advanced disease characteristics, including higher KPS, lower LDH before infusion, and fewer prior lines of therapy. Despite these potentially advantageous baseline characteristics, the ORR remained significantly lower with bendamustine. This finding suggests a potential adverse effect of bendamustine on CAR-T cell expansion and activity, emphasizing the need for further studies to confirm the impact of bendamustine on CAR-T efficacy. Notably, bendamustine has a significantly shorter half-life than fludarabine; this may reduce lymphodepleting efficacy. In allogeneic hematopoietic cell transplantation (alloHCT), peri-graft fludarabine pharmacokinetics have been linked to transplantation outcomes, suggesting that LD drug exposure is critical for engraftment. The extent to which this applies to CAR-T expansion remains unclear, but it warrants further investigation [21,27,28]. Response rates varied across CAR-T products, with axi-cel and liso-cel associated with higher ORR than tisa-cel, independent of LD regimen.

An unexpected finding was that patients 65 and younger had lower ORR and CR rates, independently of LD regimen. These findings are in line with other studies, although the literature remains limited. Dreger et al reported that responses were higher in patients aged 65 and older [29]. In a recent CIBMTR study, there were improved cumulative incidences of overall response and CR in patients 65 and older than in patients aged 18 to 54. The 55 to 64 group had lower CI of CR but similar CI of overall response at 6 and 12 months, compared to those 65 and older [30]. While this observation is intriguing, it is

likely multifactorial, and may be influenced by differences in disease burden, biology, or prior treatment history, as well as nutritional status, sarcopenia, and metabolism [31]. Additional studies are needed to further explore this association.

The increase in bendamustine-based LD use in 2021 to 2023 was largely driven by the fludarabine shortage in 2022. Among the 145 centers included, only 51 used bendamustine-based LD, and 49 of these centers had implemented it before 2021. Its use before the shortage may have been influenced by data from the JULIET trial with tisa-cel, as well as practical advantages such as its 2-day administration schedule (which is shorter than Flu/Cy's administration); improved outpatient feasibility; and potentially better resource utilization [32,33] However, during the shortage, the adoption of bendamustine was driven by the decision of the treating provider, and many centers incorporated it into practice despite the lack of robust efficacy data. Our subset analysis of patients treated during 2021 to 2023 confirmed similar findings to the overall cohort, reinforcing that bendamustine remains a viable alternative LD option.

LIMITATIONS

Several limitations should be acknowledged. In this retrospective, real-world analysis, we were unable to fully account for factors influencing LD regimen selection. Additionally, we lacked data on bendamustine exposure before LD and on the potential impact of bendamustine-containing bridging therapies. We did not assess prophylactic or preemptive strategies for CRS and ICANS; these strategies have evolved over time and could influence toxicity outcomes. We acknowledge that the effects of LD dosing were not studied and would be of interest in a future report. Furthermore, our study was limited to DLBCL, and findings may not be generalizable to other diseases, particularly acute lymphoblastic leukemia, where long-term CAR-T persistence is more strongly associated with outcomes. The smaller number of patients and shorter median follow-up in the bendamustine-based group remains an important limitation, and longer-term data are needed to fully evaluate the impact of bendamustine on survival.

CONCLUSIONS

In conclusion, while bendamustine-based LD is associated with a lower ORR and higher relapse rate than fludarabine-based LD, it provides comparable OS, with a significantly improved toxicity profile, supporting consideration of bendamustine as a practical alternative LD regimen for CAR-T therapy in DLBCL. However, the shorter follow-up duration in the bendamustine cohort warrants further investigation. Future studies should explore the impact of bendamustine on CAR-T cell expansion, long-term efficacy, and its role on other diseases.

RESEARCH DATA SHARING

Per National Institutes of Health policies, CIBMTR makes its de-identified publication analysis datasets freely available to the public for secondary analysis, while complying with all relevant global regulations about the privacy of participants and also protecting confidential and proprietary data: https://cibmtr.org/CIBMTR/Resources/Publicly-Available-Datasets#.

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