Comparative Efficacy and Safety of Beam and Team Conditioning Regimens for Autologous Stem Cell Transplantation in Lymphoma Patients

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ABSTRACT

Background. Conditioning regimens with high-dose chemotherapy and autologous stem cell transplantation (ASCT) are the mainstays of treatment in lymphoma patients. Although the most frequently used conditioning regimen is the BEAM regimen (Carmustine, Etoposide, Cytarabine, and Melphalan), and alternatives are also used in certain circumstances. The TEAM regimen (carmustine is substituted by the alkylating agent thiotepa) is one of these alternatives; however, data regarding the comparisons of efficacy and safety profiles of these 2 regimens is scarce. This study compared the outcomes of patients who received conditioning regimens with BEAM and TEAM and underwent an ASCT.

Methods. This study was conducted as a retrospective assessment of 294 patient outcomes in terms of efficacy and safety. Adult patients with lymphoma diagnosis who received BEAM or TEAM conditioning regimens and underwent an ASCT between January 1, 2016 and December 31, 2019 were included in the analyses.

Results. A total of 294 patients (median age at ASCT: 50 years, males: 60.5%, diffuse large B-cell lymphoma: 35%) were included. Eighty patients (27.2%) received the TEAM regimen, and 214 (72.8%) received the BEAM regimen. Regarding safety profiles, the thrombocyte engraftment time was significantly higher in the TEAM group ($P = .003$) and fever of unknown etiology was significantly higher in the BEAM group ($P = .042$). Also, nausea was more in the TEAM group ($P = .031$). The complete remission rate was 57.5% and 70.3% in the TEAM and BEAM regimens, respectively. The overall mortality rate was 37.3% and not significantly different between the groups (43% and 35% in the TEAM and BEAM groups, $P = .22$) over a similar median follow-up of 1667 days ($P = .28$). The 3-year survival rate was 66% and 67% and the 5-year survival rate was 52% and 58% in the TEAM and BEAM regimens, respectively, without significant difference.

Conclusion. To the best of our knowledge, this is one of the few studies in the literature that compared the TEAM and BEAM as conditioning regimens for ASCT in lymphoma patients. The 2 regimens may provide similar overall survival outcomes and have a comparable safety profile. Although the BEAM regimen may be associated with longer progression-free survival times, the difference may be covered by the similar survival after ASCT.

ADMINISTRATION of high-dose chemotherapy before autologous stem cell transplantation (ASCT) is a prevalently used approach in lymphoma treatment, particularly in

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relapsed cases after conventional chemotherapy [1]. The efficacy of conditioning regimens is associated with long-term survival, and the safety of these regimens determines the complications, morbidities, and mortality. The most frequently used intensive chemotherapy for lymphoma patients is the BEAM regimen that includes Carmustine, Etoposide, Cytarabine, and Melphalan. It is considered the standard conditioning regimen before ASCT for these patients [2].

The BEAM regimen has satisfactory efficacy and tolerability; nevertheless, it is frequently modified by replacing different agents due to difficulties in supply chains, costs, or concerns of toxicities associated with carmustine [3]. In one of these alternative regimens, carmustine is substituted by the alkylating agent, thiotepa (TEAM), and The European Society for Blood and Marrow Transplantation (EBMT) reported that it has comparable equivalency with BEAM in terms of overall and progression-free survival [4].

Currently, the number of studies comparing these 2 regimens in terms of safety and efficacy is relatively low and further studies are needed to evaluate the comparative effectiveness in real-life scenarios. Based on this background, we aimed to compare the outcomes of our patients who received conditioning regimens with BEAM and TEAM and underwent an ASCT.

MATERIAL AND METHODS

Study design and patients

This retrospective study was conducted as a chart review of 294 adult patients who underwent an ASCT in the Hematology Department of the John Hopkins Anatolian Health Center and Private Medstar Antalya Hospital in Turkey. The hospital records of patients were screened from January 1, 2016 to December 31, 2019. The lymphoma patients with complete demographic and clinical data and follow-up information were determined in the preliminary screening. The inclusion criteria to the study were having a diagnosis of lymphoma, receiving BEAM or TEAM conditioning regimens before ASCT, and undergoing an ASCT. According to study protocol, central nervous system lymphoma patients were excluded. The primary endpoints were determined as the efficacy, adverse events, and survival of these 2 regimens.

Conditioning regimens and drug selection

The doses of BEAM conditioning regimen were 300 mg/m^2 of carmustine on day -7, 2 × 100 mg/m^2 of etoposide on days -6 to -3, 2 × 200 mg/m^2 of cytarabine on days -6 to -3, and 140 mg/m^2 of melphalan on day -2, and the doses of TEAM conditioning regimen were 8 mg/kg of carmustine on day -7, 2 × 100 mg/m^2 of etoposide on days -6 to -3, 2 × 200 mg/m^2 of cytarabine on days -6 to -3, and 140 mg/m^2 of melphalan on day -2. During the study period, carmustine could not be supplied for short periods. Thiotepa was used in these periods. As a standard supportive therapy, all patients received granulocyte colony stimulating factor beginning on day +5 to neutrophil engraftment.

Statistical analysis

Descriptive statistics were presented using median and IQR (IQR 25th-75th percentile; q1-q3) for the continuous variables after controlling for the normal distribution assumptions, and the categorical variables were presented using frequency and percent. The comparisons between independent groups were made for the continuous and categorical variables using the Mann-Whitney U test with Monte Carlo method, and Pearson χ^2 and Fisher-Freeman-Holton test with Monte Carlo simulation, respectively. The post hoc comparisons for the categorical variables were reported using Benjamini-Hochberg adjusted P values. The odds ratios (OR) of risk factors for outcomes were calculated and presented in 95% CI. The survival analyses were performed with the Kaplan-Meier (product-limit) method, and Log-Rank (Mantel-Cox) test was used to compare survival curves. All analyses were performed using IBM SPSS Statistics for Windows Version 26 (IBM Corp., Armonk, New York, United States), and the type-I error level for statistical significance was considered 5% ($P < .05$).

RESULTS

A total of 294 patients were included in the analyses. Eighty patients (27.2%) received the TEAM regimen, and 214 (72.8%) received the BEAM regimen. General demographic and clinical characteristics are presented in Table 1. Accordingly, the median age at ASCT was 50 years, and 60.5% of the participants were men. Age ($P = .74$) and sex ($P = .42$) distribution were similar between treatment groups. The diagnoses included Hodgkin's lymphoma, T-cell lymphoma, diffuse large B-cell lymphoma, Mantle-cell lymphoma, follicular lymphoma, Burkitt's lymphoma, and low-grade non-Hodgkin's lymphoma. The most frequent diagnosis was diffuse large B-cell lymphoma in the whole group, seen in 35% of the cases. Although the distribution of diagnoses was similar between the treatment groups ($P = .083$), the most frequent diagnosis among patients receiving the BEAM regimen was Hodgkin's lymphoma (34.1%). The comorbidity index was also similarly distributed in conditioning regimens ($P = .51$), in which more than half of the patients had a low comorbidity index in both groups. To assess comorbidity, Hematopoietic Cell Transplantation-specific Comorbidity Index was used. On the other hand, remission status at ASCT was significantly different between the 2 groups ($P = .011$). Accordingly, post hoc analyses revealed that the >CR1 was significantly higher in the BEAM group ($P = .002$), whereas primary refractory disease was observed significantly more in the TEAM group ($P = .035$).

The distribution of adverse events and engraftment times is presented in Table 2. Number of CD34+ cells transplanted (median, range × 10^6 cells/kg) in the BEAM and TEAM group was 7.16 (2.30-51.67) and 8.21 (2.5-35.40), respectively, without any significant difference ($P = 0.852$). Analyses revealed that the neutrophil engraftment time was only marginally significant between the 2 regimens ($P = .057$); however, the thrombocyte engraftment time was significantly higher in the TEAM group ($P = .003$). Although the fever rates were similar between groups ($P = .34$), the frequency of fever of unknown etiology was significantly higher in the BEAM group (OR: 2.1, 95% CI 1.1-4.1, $P = .042$). Another adverse event that was significantly different between the conditioning regimens was nausea, observed in significantly higher proportions among the TEAM group (OR: 4.5, 95% CI 1.03-19.5, $P = .031$). The frequencies of other adverse events, including bacterial, viral, and fungal infections, gastrointestinal toxicities, mucositis, diarrhea, and

Table 1. General Demographic and Clinical Characteristics of Patients

	Total N = 294	TEAM n = 80	BEAM n = 214	*P* Value
Age at transportation, median (IQR)	50 (36/61)	51 (37/59.5)	49 (36/62)	.737
Sex, n (%)				.421
Female	116 (39.5)	35 (43.8)	81 (37.9)	
Male	178 (60.5)	45 (56.3)	133 (62.1)	
Diagnosis				0.083
Hodgkin's lymphoma	93 (31.6)	20 (25.0)	73 (34.1)	
T-cell lymphoma	35 (11.9)	10 (12.5)	25 (11.7)	
Diffuse large B-cell lymphoma	103 (35.0)	31 (38.8)	72 (33.6)	
Mantle-cell lymphoma	30 (10.2)	9 (11.3)	21 (9.8)	
Follicular lymphoma	13 (4.4)	4 (5.0)	9 (4.2)	
Burkitt's lymphoma	7 (2.4)	5 (6.3)	2 (0.9)	
Low-grade non-Hodgkin's lymphoma	13 (4.4)	1 (1.3)	12 (5.6)	
Remission status at transplantation				.011
CR1	48 (16.3)	13 (16.3)	35 (16.4)	
PR1	36 (12.2)	10 (12.5)	26 (12.1)	
>CR1	112 (38.1)	19 (23.8)	93 (43.5)	.002
>PR1	72 (24.5)	26 (32.5)	46 (21.5)	
Primary refractory	16 (5.4)	8 (10.0)	8 (3.7)	.035
Progressive disease	1 (0.3)	1 (1.3)	0 (0.0)	
Resistant relapsing	7 (2.4)	2 (2.5)	5 (2.3)	
Unknown	2 (0.7)	1 (1.3)	1 (0.5)	
Comorbidity index				.510
Low	160 (54.4)	48 (60.0)	112 (52.3)	
Moderate	78 (26.5)	19 (23.8)	59 (27.6)	
High	56 (19.0)	13 (16.3)	43 (20.1)	

BEAM, Carmustine, Etoposide, Cytarabine, and Melphalan; CR1, first complete remission; PR1, first partial remission; TEAM, carmustine is substituted by the alkylating agent thiotepa.

vomiting, were all similar between the patients who received TEAM or BEAM conditioning regimens.

The clinical follow-up of patients after the ASCT is summarized in Table 3. The median duration to discharge was 22 days in the whole group and was similar between treatment groups (P = .78). About 11.8% of the patients were hospitalized in the first 100 days, and the most frequent indication for rehospitalization was an infection in both groups (P = .50). The complete remission rate was 57.5% and 70.3% in the TEAM and BEAM regimens, respectively; however, when considering the other responses in the treatment groups, the distribution patterns were similar (P = .071). Only 17.6% of the patients received maintenance therapy after ASCT (P = .61), the relapse rate was 32.6% (P = .064), and only 1.4% of patients were diagnosed with a secondary malignancy (P = .34), which all distributed similarly between the 2 conditioning regimen groups. As maintenance therapy, rituximab for follicular lymphoma and Mantle-cell lymphoma patients, and brentuximab vedotin for high-risk Hodgkin's lymphoma patients was administered. The overall mortality rate was 37.3% and not significantly different between the groups (P = .22) over a similar median follow-up of 1667 days (P = .28). However, the duration from the first diagnosis to ASCT was significantly high among the patients in the BEAM group (18 months vs 13 months, P = .015).

Fig 1 presents the survival curves and Table 2 presents the 3- and 5-year survival rates of the treatment groups comparatively. Accordingly, the overall mortality rate was about 37% in the whole group, which was 43% and 35% in the TEAM and BEAM groups, respectively. Moreover, analyses revealed that if the survival was calculated either from the diagnosis or from the ASCT to the last follow-up or death, which corresponds to overall (P = .29) and progression-free (P = .33) survival, respectively, the 2 conditioning regimens had similar survival rates and median survival times (Table 4). In both groups, median progression-free survival could not be reached. However, if the analysis was conducted based on the duration between the first diagnosis to ASCT, which refers to time-to-progression, then the BEAM group had significantly higher durations than the TEAM group (83.1 $\pm$ 10.6 vs 73.8 $\pm$ 16.0 months, P = .033).

DISCUSSION

This study evaluated the effectiveness and safety profiles of the TEAM and BEAM regimens in lymphoma patients who underwent an ASCT. To summarize our findings, there was no treatment choice based on the age, sex, diagnosis, and comorbidity index of the patients; however, the proportion of patients at >CR1 status was higher in the BEAM group, whereas >PR1 patients were more frequent in the TEAM group. The remaining basal demographic and clinical characteristics were similar between the 2 groups. The safety profiles were evaluated based on the progression of adverse events, including fever, infections, and gastrointestinal toxicities or symptoms, and fever of unknown origin was more observed in the BEAM group,

Table 2. Adverse Events and Engraftment Times in the Whole Group and According to the Conditioning Regimens

	Total N = 294	TEAM n = 80	BEAM n = 214	*P* Value
NET, median (q1/q3)	10 (9/10)	10 (9/11)	10 (9/10)	.057
TET, median (q1/q3)	11 (10/14)	12 (11/15)	11 (10/13)	.003
Fever, n (%)				.344
No	41 (13.9)	14 (17.5)	27 (12.6)	
Yes	253 (86.1)	66 (82.5)	187 (87.4)	
Fever of unknown origin				.042
No	44 (15.0)	18 (22.5)	26 (12.2)	
Yes	249 (85.0)	62 (77.5)	187 (87.8)	2.1 (1.1-4.1)[or]
Documented bacterial infection				.651
No	220 (74.8)	58 (72.5)	162 (75.7)	
Yes	74 (25.2)	22 (27.5)	52 (24.3)	
Bacterial infection				.701
No	183 (70.9)	52 (69.3)	131 (71.6)	
Gr (-)	54 (20.9)	18 (24.0)	36 (19.7)	
Gr (+)	21 (8.1)	5 (6.7)	16 (8.7)	
Day of bacterial infection, median (q1/q3)	4 (3/6)	3 (3/5)	4 (3/6)	.231
Fungal infection, n (%)				.733
No	283 (96.3)	76 (95.0)	207 (96.7)	
Yes	11 (3.7)	4 (5.0)	7 (3.3)	
Type of documented fungal infection, n (%)				.999
Candidiasis	5 (50.0)	2 (50.0)	3 (50.0)	
Aspergillosis	5 (50.0)	2 (50.0)	3 (50.0)	
Day of fungal infection, median (q1/q3)	13 (4/24)	17 (13/22.5)	11 (3/33)	.615
Viral infection, n (%)				.999
No	283 (96.3)	77 (96.3)	206 (96.3)	
Yes	11 (3.7)	3 (3.8)	8 (3.7)	
Type of viral agent				.999
CMV	10 (83.3)	3 (100.0)	7 (77.8)	
Influenza	1 (8.3)	0 (0.0)	1 (11.1)	
Enterovirus	1 (8.3)	0 (0.0)	1 (11.1)	
Pneumonia				.999
No	284 (96.6)	77 (96.3)	207 (96.7)	
Yes	10 (3.4)	3 (3.8)	7 (3.3)	
Gastrointestinal toxicity				.113
No	8 (2.7)	0 (0.0)	8 (3.7)	
Yes	286 (97.3)	80 (100.0)	206 (96.3)	
Mucositis				.120
No	67 (22.9)	13 (16.5)	54 (25.2)	
Yes	226 (77.1)	66 (83.5)	160 (74.8)	
Nausea				.031
No	24 (8.2)	2 (2.5)	22 (10.3)	
Yes	270 (91.8)	78 (97.5)	192 (89.7)	4.5 (1.03-19.5)[or]
Diarrhea				.881
No	75 (25.5)	21 (26.3)	54 (25.2)	
Yes	219 (74.5)	59 (73.8)	160 (74.8)	
Vomiting				.103
No	33 (11.2)	5 (6.3)	28 (13.1)	
Yes	261 (88.8)	75 (93.8)	186 (86.9)	

BEAM, Carmustine, Etoposide, Cytarabine, and Melphalan; NET, Neutrophil engraftment time
[or] odds ratio (95% CI); TEAM, carmustine is substituted by the alkylating agent thiotepa; TET, thrombocyte engraftment time.

thrombocyte engraftment time was higher, and nausea was more frequent in the TEAM group. The remaining adverse events were similar between the 2 groups. On the other hand, grades of gastrointestinal toxicities were similar in both groups. Likewise, the clinical characteristics were similar in the 2 groups after ASCT. The survival analyses also showed similar mortality rates and overall and progression-free survival in the groups; however, the time-to-progression was longer in the BEAM group.

The ultimate aim of the preparative conditioning regimens before ASCT in lymphoma patients is to improve patient outcomes, both by means of efficacy and safety [5]. Currently, the

Table 3. Post-ASCT Clinical Characteristics

	Total N = 294	TEAM n = 80	BEAM n = 214	*P* Value
Duration to discharge, median (q1/q3)	22 (20/24)	22 (18/25)	22 (20/24)	.778
Rehospitalization in the first 100 d, n (%)				.837
No	253 (88.2)	68 (87.2)	185 (88.5)	
Yes	34 (11.8)	10 (12.8)	24 (11.5)	
Indication for rehospitalization in first 100 d, n (%)				.495
Infection	19 (55.9)	4 (40.0)	15 (62.5)	
Relapse	5 (14.7)	2 (20.0)	3 (12.5)	
Treatment-related factors	10 (29.4)	4 (40.0)	6 (25.0)	
Day of rehospitalization in the first 100 d, median (q1/q3)	42 (28/65)	34 (22.5/50.5)	42 (32/67)	.252
Response after ASCT, n (%)				.071
Complete remission	195 (66.8)	46 (57.5)	149 (70.3)	
Partial remission	39 (13.4)	16 (20.0)	23 (10.8)	
Stable disease	6 (2.1)	3 (3.8)	3 (1.4)	
Progressive disease	35 (12.0)	12 (15.0)	23 (10.8)	
Unknown	17 (5.8)	3 (3.8)	14 (6.6)	
Maintenance therapy after ASCT				.605
No	238 (82.4)	64 (80.0)	174 (83.3)	
Yes	51 (17.6)	16 (20.0)	35 (16.7)	
Relapse				.064
No	192 (67.4)	45 (58.4)	147 (70.7)	
Yes	93 (32.6)	32 (41.6)	61 (29.3)	
Secondary malignancy				.339
No	287 (98.6)	80 (100.0)	207 (98.1)	
Yes	4 (1.4)	0 (0.0)	4 (1.9)	
Survival				.222
Alive	180 (62.7)	45 (57.0)	135 (64.9)	
Exitus	107 (37.3)	34 (43.0)	73 (35.1)	
Follow up duration after ASCT (d), median (q1/q3)	1006.5 (466.5/1533)	1220 (317/1557)	948 (518/1494.5)	.936
Duration to relapse (d)	243 (115/448)	245 (120.5/436.5)	243 (114/520)	.869
Duration from first diagnosis to ASCT (mo)	18 (10/31)	13 (9/24.5)	18 (11/36)	.015
Follow-up duration (d)	1667 (1092/2336)	1702 (860/2084)	1655.5 (1117/2444)	.287
Mortality in the first 100 d, n (%)				.857
No	286 (97.3)	78 (97.5)	185 (88.5)	
Yes	8 (2.7)	2(2.5)	24 (11.5)	

ASCT, autologous stem cell transplantation; BEAM, Carmustine, Etoposide, Cytarabine, and Melphalan; TEAM, carmustine is substituted by the alkylating agent thiotepa.

BEAM conditioning regimen is considered the standard approach before ASCT in the treatment of lymphomas. Nevertheless, carmustine can be associated with pulmonary toxicity in some cases, and also there is limited availability in the market. Thus, novel regimens replacing it with alternative agents are being evaluated under clinical research.

Thiotepa was authorized in 2010 by the European Medicines Agency for conditioning treatment before allogeneic or autologous hematopoietic progenitor cell transplantation. Due to its enhanced capacity to cross the blood-brain barrier, thiotepa was generally preferred as a part of high-dose therapy followed by ASCT for primary central nervous system lymphomas [6]. Based on the accumulated evidence on thiotepa-based conditioning regimens, the EBMT conducted an analysis to compare thiotepa-based regimens with BEAM in diffuse large B-cell lymphoma excluding primary central nervous system lymphomas, follicular lymphoma, or Hodgkin's lymphoma and reported on the valuable importance of these novel regimens [4]. Their results showed that the progression and overall survival were similar between BEAM and TEAM regimens. Also, although not statistically significant, there were some differences regarding 3-year progression-free survival (TEAM: 49% vs BEAM: 62%) and 3-year relapse rates (TEAM: 50% vs BEAM: 37%). Similarly, our results showed that the survival rates of the 2 regimens were similar if the survival analyses were conducted with the date from the diagnosis or from the ASCT to the last follow-up or death. However, the time from the first diagnosis to ASCT was higher in the BEAM regimen. Apart from efficacy, the EBMT reported that the safety profiles of the 2 regimens were similar; however, we observed a slight difference in the fever of unknown origin and nausea, which the TEAM regimen was associated with nausea and BEAM with the fever of unknown origin.

Since the report by the EBMT, only one study directly compared the TEAM and BEAM regimens. Marchesi et al [7] compared the TEAM regimen with BEAM and fotemustine replacement of carmustine regimens in lymphoma patients who underwent ASCT after high-dose chemotherapy. The

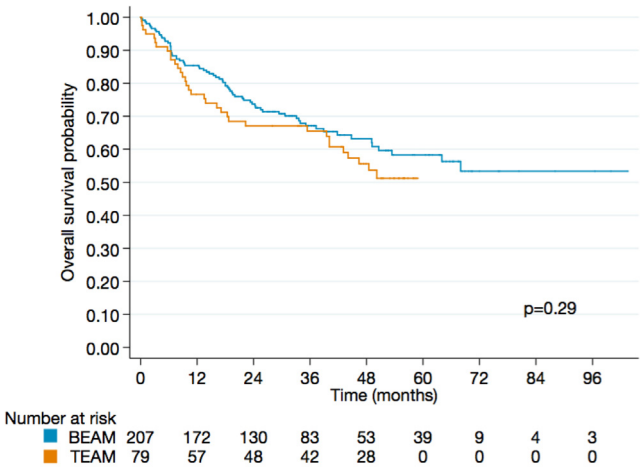

Fig 1. The survival analysis based on the overall follow-up times after autologous stem cell transplantation. BEAM, Carmustine, Etoposide, Cytarabine, and Melphalan; TEAM, carmustine is substituted by the alkylating agent thiotepa.

comparisons between TEAM and BEAM regimens showed that the BEAM conditioning regimen had a significantly higher 5-year progression-free survival than the TEAM regimen (hazard ratio: 0.52, 95% CI 0.32-0.85; $P = .009$), and the difference was stable across disease status at transplantation and the type of diagnosis of lymphoma. Also, the 5-year overall survival was better in the BEAM group (BEAM 83% vs TEAM 60%; $P = .011$). For the safety profile, the authors reported that the TEAM regimen was associated with decreased rates of severe oral mucositis. Our results were somewhat different from this study regarding the disease status at transplantation. The >CR1 status was significantly more in the BEAM group, whereas the primary refractory disease was more in the TEAM group. The differences might affect the outcomes as well, and the similarity of survival rates in our study might be associated with these differences.

Duléry et al conducted a prospective study to assess the effectivity and safety of the TEAM conditioning regimen [8]. According to their first results published in American Society of Hematology 2019, the TEAM conditioning regimen seems as an effective and safe conditioning regimen with overall survival rate 93% at day +100. As we did not find important difference about effectivity and safety profiles between TEAM and BEAM regimens, this data is also similar with our study results. Because at the end of those first results, when compared with current data, TEAM can be an alternative for a BEAM conditioning regimen.

Limitations and Strengths

The study group included patients with a variety of diagnoses in the lymphomas, which can be considered as a factor that increases the generalizability of our results to these patients. In this study, case match could not be done in 2 groups because of the limited number of patients in the TEAM group. However, the uneven distribution of the diagnoses should be evaluated cautiously. The distribution of patients in treatment groups was also not balanced; however, the routine daily practice is appropriate with the distribution and acceptable methodologically. Finally, this is one of the few studies in the literature that directly compares the outcomes of the TEAM and BEAM regimens and provides valuable data for the researchers.

CONCLUSIONS

To the best of our knowledge, our study is one of the few studies in the literature that compared the TEAM and BEAM as conditioning regimens for ASCT in lymphoma patients. Our results suggest that the 2 regimens may provide similar overall survival outcomes and have a comparable safety profile. Although the BEAM regimen may be associated with longer progression-free survival times, the difference may be covered by the similar survival after ASCT. As an overall conclusion, the BEAM regimen is the first choice for conditioning before ASCT; however, the TEAM regimen is still a valuable alternative.

Table 4. Estimated Survival Ratios After ASCT

	Dead n (%)	Alive n (%)	Estimate Survival Mean ± SE	Estimate Proportion Surviving at the 3 and 5 Year	*P* Value
Conditioning regimen*					
TEAM	34(43.0)	45(57.0)	1225.8 ± 79.38	0.66/0.52	.29
BEAM	72(34.8)	135(65.2)	2051.2 ± 103.14	0.67/0.58	
Overall	106(37.1)	180(62.9)	1994.1 ± 89.00	0.67/0.56	

Kaplan Meier Test - Log Rank (Mantel-Cox).

* Median progression-free survival could not be reached in all arms.

DATA AVAILABILITY

Data will be made available on request.

DISCLOSURE

All the authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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