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The Efficacy and Safety of Busulfan-Etoposide-Melphalan Regimen in Autologous Stem Cell Transplantation in Relapsed/Refractory Hodgkin and Non-Hodgkin Lymphoma Patients: "A Single-Center Experience"

Nüks Dirençli Hodgkin ve Hodgkin Dışı Lenfoma Hastalarında Otolog Kök Hücre Nakli Hazırlama Rejiminde Busulfan-Etoposid-Melfalan Rejiminin Etkinlik ve Güvenirliliği: "Tek Merkez Deneyimi"

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ABSTRACT

Introduction: High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) is the standard treatment for relapsed and refractory lymphoma patients. The difficulties in accessing and high cost of carmustine have led to the increased use of alternative regimen before ASCT for the treatment of lymphoma, including busulfan-based busulfan-etoposide-melphalan (BuEM) regimens.

Methods: Data of 16 Hodgkin's lymphoma and non-Hodgkin's lymphoma patients who underwent ASCT following BuEM conditioning regimen were retrospectively analyzed within the scope of the study.

Results: The median overall survival and progression-free survival during the 188 day follow-up period were found to be 93.8% and 87.1%, respectively. Neutrophil and platelet engraftment times were found to be 11 and 17 days, respectively, and the median duration of hospitalization was determined to be at 22.5 days. The prevalence of grade 3-4 mucositis was found to be at 37.6% (81.3% in total), whereas that of grade 1-4 infection was 87.5%, and grade 1-3 gastrointestinal system toxicity was found to be at 68.3%. No obvious liver and kidney toxicity were observed. Transplantation-related mortality was detected in 1 (6.25%) patient.

Conclusion: Our results suggest that a prospective study on the BuEM regimen involving a large number of cases is required.

Keywords: Autologous stem cell transplantation, Hodgkin's lymphoma, non-Hodgkin's lymphoma, conditioning regimens, BuEM

ÖZ

Amaç: Yüksek doz kemoterapi ve ardından otolog kök hücre nakli (OKHN), dirençli ve nükseden lenfoma hastaları için standart tedavidir. Karmustine ulaşımdaki zorluklar ve yüksek maliyet, Busulfan bazlı busulfan-etoposid-melfalan (BuEM) dahil olmak üzere lenfoma tedavisi için OKHN öncesinde alternatif hazırlama rejimlerinin kullanımının artmasına neden olmuştur.

Yöntemler: BuEM konsolidasyon rejimi ile OKHN uygulanan 16 Hodgkin lenfoma ve Hodgkin dışı lenfoma hastasının verileri retrospektif olarak incelendi.

Bulgular: Medyan 188 günlük takipte OS %93,8 ve PFS %87,1 olarak saptandı. Nötrofil ve trombosit engrfatman süreleri sırasıyla medyan 11 ve 17 gün oldu. Medyan hastanede kalış süresi 22,5 gün olarak belirlendi. Grade 3-4 mukozit %37,6 (total: %81,3), grade 1-4 enfeksiyon %87,5, grade 1-3 gastrointestinal sistem toksisitesi %68,3 oranında görüldü. Belirgin karaciğer ve böbrek toksisitesi görülmedi. Transplant ilişkili mortalite sadece bir hastada (%6,25) oranında görüldü.

Sonuç: Sonuçlarımız BuEM rejimi ile çok sayıda olgu içeren prospektif bir çalışmanın gerektiğini düşündürmektedir.

Anahtar Kelimeler: Otolog kök hücre nakli, Hodgkin lenfoma, Hodgkin dışı lenfoma, hazırlama rejmi, BuEM

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Introduction

Autologous stem cell transplantation (ASCT) is considered the standard treatment in patients with chemosensitive relapsed non-Hodgkin lymphoma (NHL) and relapsed/refractory (R/R) Hodgkin lymphoma (HL) following high-dose chemotherapy (1,2). In 1986, an international group called PARMA was organized involving bone marrow transplant centers from around the world. PARMA study is the first randomized study that showed the advantages of ASCT over the salvage regimen in relapsed NHL (3). Carmustine-etoposide-cytarabine-melphalan (BEAM) is the most commonly used conditioning regimen for R/R HL and NHL (4,5). Severe mucositis, gastrointestinal symptoms, and varying degrees of lung, liver, and kidney toxicities have been reported following the conditioning regimen (6-9).

Researchers have revealed that the high-dose conditioning regimen is effective and have acceptable hematological and non-hematological toxicity in ASCT in R/R lymphomas. It is clear that new treatment regimens need to be developed in several countries, including Turkey, due to the high cost of carmustine and its unavailability. Therefore, it is recommended to develop new and more effective and accessible treatment regimens with lower incidence of side effects.

The most common drug combinations such as carmustine, cyclophosphamide, etoposide, melphalan, busulfan, cytarabine, and thiotepa are used in conditioning regimens. Thus, comparative studies to BEAM have been conducted with regimens such as bendamustine-etoposide-cytarabine-melphalan (BEAM) (10,11), thiotepa-etoposide-cyclophosphamide-cytarabine-melphalan (12), lomustine-etoposide-cytarabine-melphalan (13), lomustine-cytarabine-cyclophosphamide-etoposide (14), cyclophosphamide-carmustine-etoposide (15), carmustine-etoposide-cytarabine-cyclophosphamide (BEAC) (15), busulfan-cyclophosphamide-etoposide (16,17), fotemustine-etoposide-cytarabine-melphalan (18), and mitoxantrone-etoposide-cytarabine-melphalan (19); no regimen has demonstrated significant superiority over the other.

In a study, Sakellari et al. (20) compared the effects between BEAM and busulfan-etoposide-melphalan (BuEM) regimens in patients with R/R lymphoma. BuEM regimen was well tolerated, with acceptable toxicity and without mortality, and was found to be equally effective like BEAM in NHL. In HL, it was reported that overall survival (OS) and progression-free survival (PFS) were significantly better than BEAM (20).

In this retrospective study, we aimed to report our observations regarding BuEM conditioning regimen in ASCT conducted in our center.

Methods

Sixteen patients diagnosed with R/R HL and NHL and treated with BuEM regimen as conditioning in ASCT were retrospectively analyzed. Patient characteristics included the patient's age and gender, subtype of the disease, and time period between diagnosis and transplantation; whether plerixafor was used during stem cell collection; the number of stem cells given, duration of febrile status, time to neutrophil and thrombocyte engraftment (TE), and drug-related renal, liver, and gastrointestinal toxicity and mucositis degrees; and final status in positron emission tomography/computed tomography (PET/CT) 100 days after ASCT. Neutrophil >1000/mm^3 and thrombocyte >50.000/mm^3 were accepted as engraftment levels.

The study design was approved by the Bezmialem Vakıf University Non-Interventional Research Ethics Committee (approval number: 11/230, date: 07.07.2020); however, informed consent was waived because it was a retrospective study.

Treatment Protocol

BUEM regimen was applied to all patients as conditioning before ASCT: Busulfan 9.6 mg/kg (1.6 mg/kg/12 hours per day, days -6, -5, -4), etoposide 800 mg/m^2 (400 mg/m^2/day, days -3 and -2) and melphalan 140 mg/m^2 (day, -1). Stem cells were administered at least 24 hours after the melphalan dose.

Response Criteria

Response was assessed 3 months after ASCT using the widely accepted International Working Group response criteria. Complete remission (CR) was defined as the complete regression of all detectable clinical diseases and disease-related symptoms. Response evaluation was performed by CT or PET/CT scanning in all patients 100 days after transplantation (21).

Toxicity Assessment

Regimen-related toxicities were recorded in the first 100 days. The severity and duration of oral mucositis were recorded according to the "World Health Organization" toxicity criteria (22). The other toxicities were recorded according to the Common Terminology Criteria (Version 3.0).

Statistical Analysis

In the descriptive statistics of the data, mean, standard deviation, median lowest and highest, frequency, and ratio values were used. The Kaplan-Meier method was used in survival analysis and SPSS 26.0 program in the analyses.

Results

Sixteen adult patients who underwent ASCT after BuEM conditioning regimen and diagnosed with R/R HL and NHL between January 2018 and January 2020 were included in the study. Among these patients, 5 (33.3%) were females and 11 (68.7%) were males. The median age was 61 (range: 23-75) years. Four (25%) patients were diagnosed with diffuse large B cell lymphoma, four (25%) with grade 3 follicular lymphoma, four (25%) mantle cell lymphoma, two (12.5%) HL, one marginal zone lymphoma, and one primary effusion lymphoma. The median duration from diagnosis to transplantation was 194 (range: 126-385) days (Table 1). Plerixafor was applied to four of the patients (25%) for stem cell collection due to insufficient stem cell collection with lenograstim. Stem cells were collected using only lenograstim in the other 12 (75%) patients. The characteristics of the patients before HSCT are summarized in Table 1.

The median time until neutrophil engraftment (NE) was 11 (range: 10-15) days and median time until TE was 17 (range: 13-77) days. The median number of stem cells transfused to the patients was 6.3

(range: 3.6-13) x10^6/kg. The median usage time of granulocyte colony-stimulating factor (G-CSF) (lenograstim) was 7.5 (range: 5-14) days.

All patients were in CR before transplantation. Remission control was performed with PET/CT 100 days after the transplant, except for one patient who died of post-transplant-related mortality. According to PET/CT results, 14 patients (87.25%) had CR and one patient (6.25%) had recurrence. One patient relapsed 200 days after ASCT. The median follow-up period after ASCT was 188 days (range: 14-775 days, 95% CI).

Four patients had grade 1, five grade 2 (31.3%), two grade 3 (12.5%), and five grade 4 (31.3%) pneumonia and sepsis. Only one patient had septic shock due to deep neutropenia. Transient grade 1 renal and liver toxicity developed in only two (12.5%) patients. The remaining 14 (87.5%) patients did not exhibit liver and renal toxicities. Moreover, patients were followed up for mucositis. Seven (43.8%) patients had grade 1, five grade 2 (31.3%), and one (6.3%) grade 3 mucositis. Grade 4 mucositis was not observed in any of the patients, and mucositis was not detected in three (18.8%) patients. No gastrointestinal toxicity was observed in five patients (31.3%); however, four patients had grade 1 (25%), five patients (31.3%) grade 2, and two patients grade 3 (12.5%) gastrointestinal toxicity such as nausea, vomiting, and diarrhea. Grade 4 GI side effects were not observed in any patient. The median duration of hospitalization of the patients was 22.5 (range: 19-27) days. Post-transplant response status and non-hematological toxicities are shown in Table 2.

Discussion

The BEAC conditioning regimen was preferred in the PARMA study, which was the first randomized study to show the superiority of ASCT over salvage chemotherapy in relapsed NHL patients following high-dose chemotherapy. In this study, the 5-year event-free survival and OS were 12% and 32% in the salvage chemotherapy group and 46% and 53% in the ASCT group, respectively (3). Furthermore, in various studies, the superiority of ASCT over conventional chemotherapy was confirmed (4,23,24). Researchers agree that a conditioning regimen with a high response rate and acceptable hematologic and non-hematologic toxicity should be determined.

However, commonly used conditioning regimens have their pros and cons, and the available literature provides limited data demonstrating the superiority of any regimen for lymphomas. Among these factors, BEAM regimen has been the leading and most widely used regimen in both HL and NHL. Moreover, its superiority has been shown in various studies (25-28). However, severe chemotherapy-induced mucositis, gastrointestinal symptoms, and varying degrees of lung, liver, and renal toxicities result in the need for new conditioning regimens (6-9). Experimental data show that the combination of busulfan and nucleoside activates a DNA damage response in lymphoma cell lines (29). Busulfan is one of the oldest alkylating agents, which is highly lipophilic and active in various malignancies such as multiple myeloma and lymphomas (30).

Table 1. The characteristics of the patients before ASCT

		Min-Max	Median	Mean ± SD/(n, %)
Age		23.0-75.0	61.5	54.3±16.9
Gender	Female	-	-	5 (31.3%)
	Male	-	-	11 (68.7%)
Histology; n (%)				
Diffuse large B cell lymphoma		-	-	4 (25.0%)
Follicular lymphoma		-	-	4 (25.0%)
Hodgkin's lymphoma		-	-	2 (12.5%)
Mantle cell lymphoma		-	-	4 (25.0%)
Marginal zone lymphoma		-	-	1 (6.25%)
Primary effusion lymphoma		-	-	1 (6.25%)
Usage of plerixafor	(-)	-	-	12 (75.0%)
	(+)	-	-	4 (25.0%)
Stage at the time of diagnosis	Stage 2	-	-	3 (18.7%)
	Stage 3	-	-	1 (6.3%)
	Stage 4	-	-	12 (75.0%)
Stage of disease before salvage regimen	Stage 2	-	-	3 (18.8%)
	Stage 3	-	-	4 (25.0%)
	Stage 4	-	-	9 (56.2%)
Status before ASCT	CR	-	-	16 (100.0%)
N of pretransplant line of chemotherapy				
1st line		-	-	5 (31.3%)
>1st line		-	-	11 (68.7%)

ASCT: Autologous stem cell transplantation, CR: complete remission, Min: minimum, Max: maximum, SD: standard deviation

Table 2. Post-transplant response status and non-hematological toxicities

		Min-Max	Median	Mean ± SD/(n,%)
Status after 3 months after ASCT	CR	-	-	14 (87.25%)
	Relapsed	-	-	1 (6.25%)
	Exitus	-	-	1 (6.25%)
Follow-up duration after ASCT (days)		14.0-775.0	188.0	229.0±150.0
Time to neutrophil engraftment		10.0-15.0	11.0	11.3±1.3
Time to platelet engraftment		13.0-77.0	17.0	23.7±21.2
Number of stem cells (x10^6/kg)		3.6-13.0	6.3	7.0±2.5
Usage of G-CSF (days)		5.0-14.0	7.5	8.3±3.1
Duration of febrile status (days)		2.0-11.0	4.5	5.8±3.1
Infection	Grade 1	-	-	4 (25.0%)
	Grade 2	-	-	5 (31.25%)
	Grade 3	-	-	2 (12.5%)
	Grade 4	-	-	5 (31.25%)
Renal toxicity	(-)	-	-	14 (87.5%)
	(+) (grade 1)	-	-	2 (12.5%)
Mucositis	Grade 0	-	-	3 (18.75%)
	Grade 1	-	-	7 (43.75%)
	Grade 2	-	-	5 (31.25%)
	Grade 3	-	-	1 (6.25%)
Liver toxicity	(-)	-	-	14 (87.5%)
	(+)	-	-	2 (12.5%)
Gastrointestinal toxicity	Grade 0	-	-	5 (31.25%)
	Grade 1	-		4 (25.0%)
	Grade 2	-	-	5 (31.25%)
	Grade 3	-	-	2 (12.5%)
Hospitalization (days)		19.0-27.0	22.5	22.8±2.7
Last status	CR	-	-	13 (81.25%)
	Exitus	-	-	1 (6.25%)
	Relapsed	-	-	2 (12.5%)

ASCT: Autologous stem cell transplantation, G-CSF: granulocyte colony-stimulating factor, CR: complete remission, Min: minimum, Max: maximum, SD: standard deviation

Since BEAM is the most commonly used conditioning regimen in ASCT, comparative studies in the literature were conducted with BEAM regimen. In our study, BuEM protocol was used as conditioning in ASCT. The median follow-up period after ASCT was 188 days, and the median PFS and OS have not yet been obtained. PFS in month six was 87.1%, and the OS was 93.8% (Figure 1, 2).

As studied by Sakellari et al. (20) in a comparative study of BEAM and BuEM regimens, the 2 year OS with the BEAM regimen was 82.4% in HL and 77.6% (p=0.3) in NHL patients. The 2 year PFS was 64.8% in HL and 57.8% (p=0.5) in NHL. With the BuEM regimen, the 2 year OS in HL patients was 96.2% and PFS was 85.1%, whereas in NHL patients, it was 56.6% and 41%, respectively. OS was superior in HL patients compared to the BEAM arm in the BuEM cohort (2 year OS of 96.2% versus 77.3%, p=0.05). In particular, reduced risk of relapse was reported in HL patients receiving BuEM compared to NHL patients. It was observed that the same significant difference in PFS was reached in patients with chemoresistant HL (HL, 55.6%, and NHL, 9.1%; p=0.0005) (20).

In our study, the patients were transfused with CD34 + cells at a median number of 6.3x10^6 kg. In the study of Sakellari et al. (20), median numbers of 4.3 and 5.7x10^6 of CD34 + cells (p=0.054) were administered in the BEAM and BuEM arms, respectively. The BuEM regimen was generally well tolerated and engraftment was rapid and permanent in the majority of patients.

The importance of time to NE findings is widely accepted. In our study, the median time to NE was 11 days and time to TE was 17 days. In the study of Sakellari et al. (20), the median times to NE for the BuEM and BEAM regimen were 10 and 9 days and median times to TE were 13 and 11 days, respectively. In this study, a faster NE was found in BEAM cohort; however, the real difference was a 1 day delay in the BuEM arm (BEAM, 9.0, vs BuEM, 10.0 days; p=0.05). Additionally, platelet engraftment was

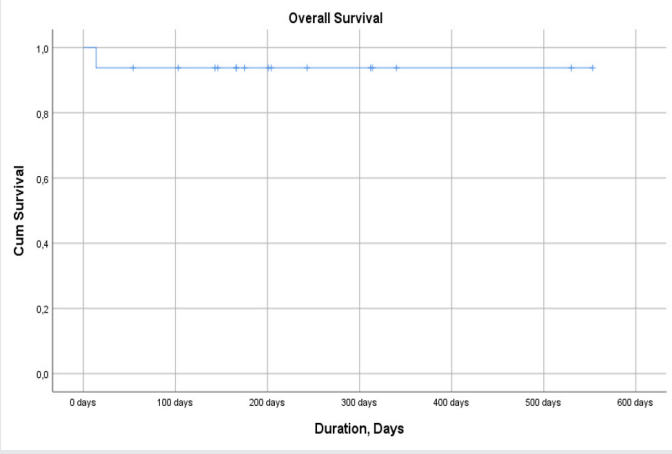

Figure 1. Overall survival (93.8%)

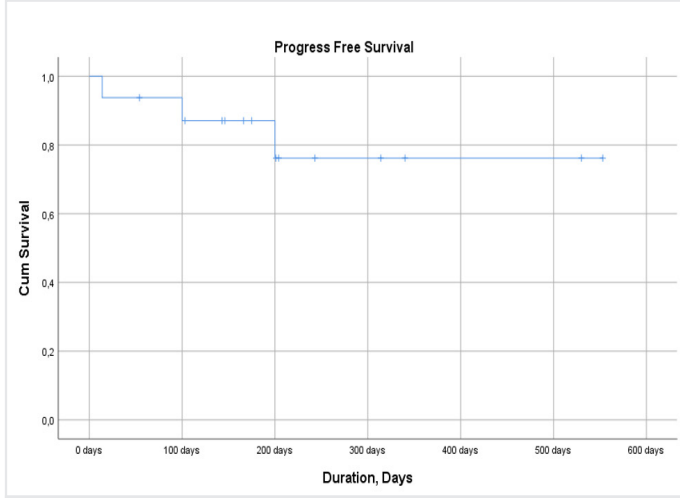

Figure 2. Progression-free survival (87.1%)

2 days earlier in the BEAM cohort (11.0 vs 13.0 days; p=0.025) (20). In studies comparative with BEAM, times to NE and TE were found to be similar (10-19). Times to engraftment, OS, and PFS in various studies are summarized in Table 3.

In our study, median G-CSF administration time was 7.5 days. Paradoxically, in Sakellari et al.'s (20) study, there was a significantly less need for G-CSF (11.0 vs 9.0 days) in the BuEM arm, although time to NE was longer in the BuEM arm than in the BEAM arm (p<0.001). In the present study, the median hospitalization duration was 22.5 days. In the study of Sakellari et al. (20), patients were hospitalized for 21 (BEAM) and 22 (BuEM) days (p=0.074). These results were consistent with those of our study. In several studies, comparative with BEAM, duration of hospitalization ranged from 19 to 23 days in the BEAM arm (10-19).

In our study, infection was not observed in two patients. However, 14 patients developed an infection (87.5%); 56.3% of them had grade 1-2 and 43.8% had grade 3-4 infection. In the study of Sakellari et al. (20), the BEAM regimen was associated with a low infection incidence (p=0.006); however, grade 3-4 infection was not observed in the groups. In our study, our infection rates were found to be higher. In comparative studies with BEAM regimen, the lowest rate for infection was 47.2%, whereas the highest rate was 100% (15,16).

In our study, the total GIS toxicity (vomiting and diarrhea) was 68.8%, whereas it was 12.5% in grade 3 toxicity. Different GIS toxicities were seen in comparative studies with the BEAM regimen. In various studies, GIS toxicity rates ranged from 39% to 97.7% with the BEAM regimen (10-19). In these studies, only lomustine had an effect on prolonged GIS symptoms, and similar rates of GIS toxicity were observed in others (13).

In the present study, grade 1 renal and liver toxicity such as mild transaminase and creatinine elevation was observed in only two patients. Sinusoidal obstruction syndrome (SOS) cases were not observed. In the study of Sakellari et al. (20), a total of 6% and 15.9% kidney toxicity was observed in BuEM and BEAM arms, respectively, whereas 72% and

Table 3. Times to engraftment, OS and PFS in various studies

Name of study	Time to NE (median, range)	Time to PE (median, range)	OS (2 years)	PFS (2 years)
Our study	11 (10-15)	17 (13-77)	93.8	87.1
BeEAM[10,11]	10 (0-98)	11 (0-210)	NR (30)	72 (30)
TECAM (NHL/HL)[12]	12 (9-72)	17 (8-935)	61.8/82.8	50/49
LEAM[13]	11 (10.4-11.2)	12 (1.5-14)	86	69
LACE[14]	10 (7-28)	13 (6-34)	46	37
BEAC[15]	11 (8-14)	12 (7-26)	81.8	67.6
CBV[15]	10.5 (9-12)	11.5 (9-18)	68.8	43.8
BuCyE[16,17]	12 (8-14)	14.5 (10-32)	72.1	70.1
FEAM[18]	10 (6-NR)	13 (7-NR)	86.1	73.1
NEAM[19]	12.3 (3-50)	13.5 (0-175)	64.2	NR
BuEM[20]	10 (8-31)	13 (6-150)	79.8	65.6
BEAM[20]	9 (6-20)	11 (3-25)	76.7	63.2

BEAM: BCNU (carmustine)-etoposide-cyatarabine- melphalan, TECAM: thiotepa-etoposide, cyclophosphamide-cytarabine-melphalan, LEAM: lomustin-etoposide-cytarabine-melfalan, LACE: lomustine-cytarabine-cyclophosphamide-etoposide, BEAC: BCNU (carmustine)-etoposide-cytarabine-cyclophosphamide, CBV: cyclophosphamide-carmustine-etoposide, BuCyE: busulfan-cyclophosphamide-etoposide, FEAM: fotemustine-etoposide-cytarabine-melfalan, NEAM: mitoxantrone-etoposide-cytarabine-melphalan, BuEM: busulfan-etoposide-melphalan, OS: overall survival, PFS: progresion free survival, NR: not reached

Table 4. Non-hematological toxicities in our and various studies

Name of study	Infection (%)	GIS toxicity (%)	Renal toxicity (%)	Liver toxicity (%)	Mucositis (%)	TRM (%)
Our study	87.5	68.8	12.5	12.5	81.3	6.25
BeEAM[10,11]	78.2	54	27.9	15	87	3.3
TECAM[12]	74	*	16	*	85.7	2.8
LEAM[13]	*	50	5	8	30	4
LACE[14]	*	39	*	*	53	9
BEAC[15]	31.2	62.3	*	61	22.1	0
CBV[15]	56.2	50	*	81.5	25	0
BuCyE[16,17]	77.4	54.8	*	*	38.7	6.5
FEAM[18]	71.3	28.3	0.7	3	76.8	3.8
NEAM[19]	23.2	*	20.3	66.7	100	2.9
BuEM[20]	89.6	60	6	72	98	0
BEAM[20]	65.1	97.7	15.9	52.3	93.2	3.4

*No data, BEAM: BCNU (carmustine)-etoposide-cyatarabine-melphalan, TECAM: thiotepa-etoposide, cyclophosphamide-cytarabine-melphalan, LEAM: lomustin-etoposide-cytarabine-melfalan, LACE: lomustine-cytarabine-cyclophosphamide-etoposide, BEAC: BCNU (carmustine)-etoposide-cytarabine-cyclophosphamide, CBV: cyclophosphamide-carmustine-etoposide, BuCyE: busulfan-cyclophosphamide-etoposide, FEAM: fotemustine-etoposide-cytarabine-melfalan, NEAM: mitoxantrone-etoposide-cytarabine-melphalan, BuEM: busulfan-etoposide-melphalan, GIS: gastrointestinal system, TRM: transplant related mortality

53% liver toxicity were observed at the same time. In the BEAM group, grade 3 liver toxicity was 3.4% and 18.0% in the BuEM group. A moderate case of SOS was observed in the BuEM cohort, which was resolved with defibrotide (20).

Significant cardiac toxicity was not reported in our study and in thatzof Sakellari et al. (20) In our study, all degrees of mucositis were seen in 81.2% of our patients. Only 6.3% of them were grade 3. Grade 4 mucositis was not noted. In Sakellari et al.'s (20) study, the BEAM arm was associated with significantly less severe (grade 3-4) mucositis ($p<0.001$). It was noted that only 2% of patients receiving BuEM had grade 4 mucositis. Sakellari et al. (20) recorded no mortality in the BuEM cohort. In our study, one patient (6.25%) died due to post-transplant septic shock.

Information obtained from studies comparing the toxicity and efficacy profiles of different high-dose regimens applied in NHL and HL treatment is limited. All of these studies were done comparatively with the BEAM regimen. Although the results were not homogeneous, it was observed that the side-effect profile was generally similar. Grade 1-4 non-hematological toxicities seen in our study and in various studies are summarized in Table 4.

Study Limitations

The limitations of our study were the small number of cases and the short follow-up period.

Conclusion

Within the limitations of a retrospective analysis, we concluded that the BuEM conditioning regimen exhibited a similar efficacy and toxicity profile with the commonly used BEAM and other new protocols, with neither regimen significantly superior to the other. Although the median follow-up time of 24.2 months was relatively short in our study, our results appear comparable to those of previous studies. Our results recommend considering BuEM as an alternative ASCT conditioning regimen in high-risk lymphoma patients. Large, prospective clinical studies should be conducted to validate our results. The fact that Busulfan, which is an effective agent in lymphoma treatment, is more accessible and low cost compared to carmustine stands out as another reason for preference. BuEM conditioning regimen is promising for patients with refractory and recurrent aggressive lymphomas.

Ethics Committee Approval: The study design was approved by the Bezmialem Vakıf University Non-Interventional Research Ethics Committee (approval number: 11/230, date: 07.07.2020).

Informed Consent: Informed consent was waived because it was a retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - A.E., A.T.; Concept - A.E.; Design - A.E.; Data Collection or Processing - A.E.; Analysis or Interpretation - A.E., A.T.; Literature Search - A.E., A.T.; Writing - A.E.

Conflict of Interest: No conflict of interest was declared by the authors.

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