Hematology/Oncology and Stem Cell Therapy

Volume 15 | Issue 4 Article 6

Comparison of mitoxantrone–melphalan and BEAM conditioning regimens in patients with lymphoma

Ahmet Kursad Gunes
Ankara City Hospital, Department of Hematology, Ankara, Turkey

Istemi Serin
University of Health Sciences, Istanbul Training and Research Hospital, Department of Hematology, Istanbul, Turkey, serinistemi@hotmail.com

Ilknur Demir
Gaziantep Abdulkadir Yuksel State Hospital, Gaziantep, Turkey

Serpil Sarifakiogullari
Giresun University, Faculty of Medicine, Department of Hematology, Giresun, Turkey

Salih Sertac Durusoy
Van Training and Research Hospital, Department of Hematology, Van, Turkey

See next page for additional authors

Recommended Citation

Gunes, Ahmet Kursad; Serin, Istemi; Demir, Ilknur; Sarifakiogullari, Serpil; Durusoy, Salih Sertac; Akkurt, Dervis Murad; Ince, Idris; Ozkan, Gulkan; Cinli, Tahir Alper; and Pehlivan, Mustafa (2022) "Comparison of mitoxantrone–melphalan and BEAM conditioning regimens in patients with lymphoma," *Hematology/Oncology and Stem Cell Therapy*: Vol. 15 : Iss. 4 , Article 6.
Available at: https://doi.org/10.1016/j.hemonc.2021.03.005

Comparison of mitoxantrone–melphalan and BEAM conditioning regimens in patients with lymphoma

Authors

Ahmet Kursad Gunes, Istemi Serin, Ilknur Demir, Serpil Sarifakioglullari, Salih Sertac Durusoy, Dervis Murad Akkurt, Idris Ince, Gulkan Ozkan, Tahir Alper Cinli, and Mustafa Pehlivan

ORIGINAL RESEARCH REPORT

Comparison of Mitoxantrone–Melphalan and BEAM Conditioning Regimens in Patients with Lymphoma

Ahmet Kursad Gunes [a], Istemi Serin [b,*], Ilknur Demir [c], Serpil Sarifakiogullari [d], Salih Sertac Durusoy [e], Dervis Murad Akkurt [f], Idris Ince [g], Gulkan Ozkan [h], Tahir Alper Cinli [b], Mustafa Pehlivan [f]

[a] Ankara City Hospital, Department of Hematology, Ankara, Turkey
[b] University of Health Sciences, Istanbul Training and Research Hospital, Department of Hematology, Istanbul, Turkey
[c] Gaziantep Abdulkadir Yuksel State Hospital, Gaziantep, Turkey
[d] Giresun University, Faculty of Medicine, Department of Hematology, Giresun, Turkey
[e] Van Training and Research Hospital, Department of Hematology, Van, Turkey
[f] Gaziantep University, Faculty of Medicine, Department of Hematology, Gaziantep, Turkey
[g] Dr. Ersin Aslan Training and Research Hospital, Department of Hematology, Gaziantep, Turkey
[h] Istanbul Hamidiye Sisli Etfal Training and Research Hospital, Department of Hematology, Istanbul, Turkey

Abstract

Objective/Background: Lymphoma is seen as a highly treatable and curable malignancy with aggressive treatment methods. Efficacy is often limited by toxicity and many patients need alternative treatment strategies as they cannot tolerate existing high cytotoxic approaches. Our aim is to compare BEAM [carmustine (BCNU), etoposide, cytarabine (ARA-C, cytosine arabinoside), and melphalan] and mitoxantrone–melphalan (Mx-Mel) regimens utilized in our patients with a diagnosis of lymphoma who underwent autologous stem cell transplantation (ASCT), and to demonstrate that the Mx-Mel regimen has similar but less toxic results than the BEAM regimen we have been using frequently as standard conditioning regimen.

Methods: **A total of 101 patients with lymphoma who underwent ASCT were included in our study. The BEAM regimen included BCNU, etoposide, ARA-C, and melphalan. The Mx-Mel regimen included mitoxantrone and melphalan.**

Results: **Of 101 patients included in the study, 60 (59.4%) received BEAM and 41 (40.6%) received Mx-Mel (40.6%) conditioning regimen. The median time to neutrophil engraftment was 10 (range: 9–20) days and 12 (range: 9–12) days in the BEAM and Mx-Mel arms, respectively; it was statistically significantly shorter in the BEAM arm ($p = .001$).**

Conclusion: **This study demonstrates that the Mx-Mel regimen has similar efficacy and toxicity compared with the BEAM regimen. Although time to neutrophil engraftment was shorter in the BEAM arm, it did not result as significant transplant-related complications between the two regimens. The Mx-Mel regimen is seen as a good alternative with low toxicity and high efficacy.**

Keywords: Autologous stem cell transplantation, BEAM, Lymphoma, Mitoxantrone, Prognosis

1. Introduction

Hodgkin lymphoma (HL) represents about 11% of all lymphomas [1]. This disease manifests with a distribution with two peaks (young adults, and patients who are 55 years old and older) [1,2]. With the advances in HL approaches, a very important step has been made in the treatment of patients diagnosed who are aged 60 years or younger. Despite these optimistic results, 5–10% of all cases are in the relapsed/refractory (R/R) group, including patients who achieved complete remission (CR) after initial treatment [2].

Non-Hodgkin lymphoma (NHL) represents a heterogeneous group of diseases, mostly of B-cell origin. B-cell NHL is generally classified into two

Received 16 December 2020; revised 20 March 2021; accepted 27 March 2021.
Available online 23 December 2022

* Corresponding author at: University of Health Sciences, Istanbul Training and Research Hospital, Department of Hematology, Org.Nafiz GURMAN Cad. 34098, Fatih/Istanbul, Turkey.
E-mail address: serinistemi@hotmail.com (I. Serin).

https://doi.org/10.1016/j.hemonc.2021.03.005

broad subsections: aggressive and indolent lymphomas. The most common subtypes of these lymphomas are diffuse large B-cell lymphoma and follicular lymphoma [3]. NHL is seen as a highly treatable and curable malignancy, specifically with aggressive treatment methods. However, efficacy is often limited by toxicity and many patients need alternative treatment strategies as they cannot tolerate existing high cytotoxic approaches.

For both lymphoma subtypes in primary refractory disease, conventional salvage therapy in patients with responding disease, despite lack of CR, and followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT) is the standard approach. Consolidation with ASCT after salvage chemotherapy in patients with R/R NHL can provide curative therapy [4]. An important study based on ASCT, Philip et al. [5] compared salvage therapy with ASCT in patients diagnosed with high-grade B- and T-cell lymphomas. After 5 years of follow-up, the overall survival (OS) was 53% in the ASCT group and 32% in the salvage therapy group ($p = .038$). In aggressive NHL, frontline ASCT is also one of the topics discussed.

In the study by Schmitz et al. [6], which is one of the basic ASCT studies dealing with the chemosensitive patient group in the first relapse in HL, the 3-year progression-free survival (PFS) was 55% in the ASCT arm versus 34% in the salvage therapy arm. There was no significant difference in terms of OS. Although frontline consolidative ASCT is also discussed in advanced stage patients in HL, it does not provide an OS advantage [7].

The most widely used conditioning regimens in patients with lymphoma are carmustine (BCNU), etoposide, cytarabine (ARA-C), and melphalan (BEAM); carmustine, etoposide, cytarabine, and cyclophosphamide (BEAC) [8]; busulfan, cyclophosphamide, and etoposide (BUCYVP-16) [9]; busulfan, cyclophosphamide, etoposide (BuCyE) [10]; mitoxantrone–melphalan (Mx-Mel) [11]; and combination regimens with total body irradiation [12]. Besides, there are such regimens similar to BEAM as lomustine, etoposide, cytarabine, and melphalan (LEAM) [13], in which lomustine is used instead of BCNU, BeEAM [14], in which bendamustine is used, and FEAM [15], in which fotemustine is used. In the ASCT treatment process, the main goal should be to achieve maximum effect with low toxicity. We see that many studies are performed for this purpose.

Our aim in this study is to compare BEAM and Mx-Mel regimens used in our patients with a diagnosis of NHL and HL who underwent ASCT, and to show that the Mx-Mel regimen has similar but less toxic results compared with the BEAM regimen we have been using frequently as standard conditioning regimen. There were several important reasons in choosing the Mx-Mel regimen while conducting our study. Our experience with Mitoxantrone is quite sufficient due to the acute myeloid leukemia induction therapies. The use of mitoxantrone as another anthracycline was also a suitable option for all patients with lymphoma, as doxorubicin was preferred in the first-line treatment regimens for both HL and NHL.

2. Materials and methods

2.1. Patients

A total of 101 patients who underwent ASCT with the diagnosis of lymphoma were included in our retrospective study in the Bone Marrow Transplantation Unit at Gaziantep University between 2014 and 2019. The patients were evaluated retrospectively; Mx-Mel or BEAM regimen was used according to treating physician's preference.

Patients who are at least 18 years old, have a chemosensitive disease, and achieved at least partial response with salvage therapy, ejection fraction of 55% and above, creatinine clearance of 60% and above, adequate lung/liver functions, and Eastern Cooperative Oncology Group (ECOG) performance status 0–2 were included in the study. Patients with central nervous system involvement, chemorefractory disease, and who received BEAM as salvage therapy were excluded from our study. Responses to the initial induction chemotherapy, salvage chemotherapy, and SCT were evaluated according to the International Workshop Criteria (Cheson Criteria) [16]. The Common Terminology Criteria for Adverse Events (CTCAE 4.0) Toxicity Scale is specifically used to rate the complications caused by chemotherapy during the hospitalization process of SCT. In all patients, the maximum recommended cumulative dose of anthracycline was calculated and none of the patients received more than the dose of anthracycline allowance. The study was approved by the Toros University (Mersin, Turkey) institutional review and local ethics committee. Ethical committee approval was received (Approval date and number: 18.01.2019–1645) and the patients and control patients gave informed written consent before the beginning of the study. The experimental procedures were based on the Declaration of Helsinki and relevant institutional regulations.

Transplant procedure and conditioning regimen

The BEAM regimen included BCNU at 300 mg/m^2 on Day −7, etoposide at 200 mg/m^2 and ARA-C at 200 mg/m^2 BID on Days −6 to −3, and melphalan at 140 mg/m^2 on Day −2. The Mx-Mel regimen included mitoxantrone 60 mg/m^2 at Day −5 and melphalan 180 mg/m^2 at Day −2. The total dose of mitoxantrone was given as three individually divided doses with 1-hour intervals on the same day. Collected CD34-positive cells were re-infused on Day 0. The protocols of conditioning regimens are summarized in Table 1.

Chemotherapy (cisplatin-based or gemcitabine-based therapy) and granulocyte colony-stimulating factor (G-CSF; 5–10 μg/kg/day) or plerixafor plus G-CSF (10 μg/kg/day) were used as a mobilization process.

All patients received G-CSF 5 μg/kg from Day + 5 of ASCT until neutrophil engraftment. All patients received levofloxacin at 500 mg/day, fluconazole at 300 mg/day, and valacyclovir at 500 mg/day until neutrophil engraftment. Tumor lysis syndrome prophylaxis was applied from Day −7 to −1 with allopurinol 300 mg/day. Packed red cell concentrates were given to maintain hemoglobin > 7.0 g/dL. Platelet concentrates were given when platelet count was < 10 × 109/L.

Neutrophil engraftment was defined as the day of absolute neutrophil count ≥ 0.5 × 10^9/L, while platelet engraftment was defined as the first of 3 consecutive days that platelet count was ≥ 20 × 10^9/L with no requirement for platelet transfusion.

3. There were no changes to transplant-related supportive care, antimicrobial prophylaxis, and/or growth factor support during that time period.

3.1. Outcome evaluation

Transplant-related mortality (TRM) was defined as any death unrelated to relapse or progressive disease during the first 100 days after the transplant. PFS was considered as the time from the date of transplant to the beginning of the next treatment, disease progression, relapse, death, or last follow-up. OS was defined as the time from ASCT until death or the date the patient was last known to be alive. The cut-off date for survival analysis for all patients was June 30, 2019.

3.2. Statistical analysis

The SPSS version 23 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Kolmogorov–Smirnov and Shapiro–Wilk tests were used to analyze the normal distribution of data. Those with normal distribution in numerical variables were summarized as mean ± standard deviation, and those without normal distribution were summarized as median (minimum–maximum). Number and percentage expressions were used for categorical variables. In the analysis of categorical variables, chi-square test was used. Mann–Whitney U test was used for the analysis of the differences between nonparametric independent variables, and t test was used for the analysis of parametric variables. Survival analysis and graphics were performed by Kaplan–Meier analysis. Survival differences were analyzed by the log-rank test. Survival-related findings were evaluated by univariate analysis, and risk factors that were found to be significant were analyzed using the multivariate Cox regression model. In statistical analysis, $p < .05$ was considered as significant.

4. Results

Of 101 patients included in the study, 60 (59.4%) received BEAM and 41 (40.6%) received Mx-Mel conditioning regimen. In the BEAM arm, 34 (56.3%) patients were diagnosed with NHL and 26 (43.3%) with HL. In the Mx-Mel arm, 24 (58.5%) patients were diagnosed with NHL and 17 (41.5%) with HL. There was statistically no significant difference in disease distribution ($p = .85$). Hematopoietic stem cell transplantation specific comorbidity indexes of the patient subgroups were also calculated. In the BEAM arm, median value was 2 (range: 0–8), while in the Mx-Mel arm, it was 3 (range: 0–8). There was statistically no significant difference between the two groups (Table 2).

There was statistically no significant difference between the two treatment subgroups in terms of

Table 1. Protocols of Conditioning Regimens.

BEAM protocol		Mitoxantrone–melphalan protocol	
BCNU (300 mg/m^2)	(Day −7)	Mitoxantrone (60 mg/m^2)	(Day −5)
Etoposid (200 mg/m^2/day)	(Days −6, −5, −4, −3)	Melphalan (180 mg/m^2)	(Day −2)
ARA-C (200 mg/ m^2 BID)	(Days −6, −5, −4, −3)		
Melphalan (140 mg/m^2)	(Day −2)		

Note. BEAM = BCNU, etoposide, ARA-C, and melphalan; BID = twice daily.

Table 2. Baseline Patient and Disease Characteristics.

		Total patients	BEAM	Mx-Mel	*p*
Patients		101	60	41	
Age, median (range)	years	45 (18−69)	46 (18−69)	43 (18−69)	0.52
Sex	Male	68	44 (73.3)	24 (58.5)	0.11
	Female	33	16 (26.7)	17 (41.5)	
Histologic subtype	NHL	58	34 (56.3)	24 (58.5)	0.85
	HL	43	26 (43.3)	17 (41.5)	
Stage	I−II	18	13 (21.7)	5 (12.2)	0.22
	III−IV	83	47 (78.3)	36 (87.8)	
Bulky disease	Yes	9	3 (5)	6 (14.6)	0.09
	No	92	57 (95)	35 (85.4)	
Bone marrow involvement	Yes	33	22 (36.7)	11 (26.8)	0.30
	No	68	38 (62.3)	30 (72.2)	
ECOG performance status	0		49 (81.7)	32 (78)	0.87
	1		8 (13.3)	7 (17.1)	
	2		3 (5)	2 (4.9)	
Disease status at transplant	PR	19	10 (16.7)	9 (22)	0.50
	CR	82	50 (82.3)	32 (78)	
HCT-CI, mean (range)		2 (0−8)	2 (0−8)	3 (0−8)	0.91

Note. Data are presented as *n* (%) unless otherwise indicated. BEAM = BCNU, etoposide, ARA-C, and melphalan; CR = complete response; ECOG = Eastern Cooperative Oncology Group; HCT-CI = hematopoietic stem cell transplantation specific comorbidity index; HL = Hodgkin lymphoma; Mx-Mel = mitoxantrone−melphalan; NHL = non-Hodgkin lymphoma; PR = partial response.

the stages of diagnosis, presence of bulky disease, presence of bone marrow involvement, ECOG scores, and treatment response at the time of transplant of the patients included in the study ($p > .05$; Table 2).

There was statistically no significant difference between the mobilization regimes of the patients ($p = .57$). The median stem cell count was 9×10^6/kg in both arms. Times to engraftment of the patients were evaluated separately in both subgroups. The median time to neutrophil engraftment was 10 (9−20) days and 12 (9−12) days in the BEAM and Mx-Mel arms, respectively; it was statistically significantly shorter in the BEAM arm ($p = .001$). There was statistically no significant difference between the two groups in terms of platelet engraftment ($p > .05$; Table 3).

When the adverse effect profile was examined, there was statistically no significant difference between the two groups in terms of number of febrile neutropenic attacks, mucositis, gastrointestinal, renal, and hepatotoxicity. Febrile neutropenia attacks were analyzed by dividing into subgroups: fever of unknown origin, proven infections (bacteremia, pneumonia, gastrointestinal infection, and urinary infection). There was no statistical difference in subgroups between the two treatment arms ($p > .05$; Table 3).

Considering the transplant-related 100-day mortality, it was seen that a total of three patients (two in the BEAM arm and one in the Mx-Mel arm) were exitus. There was statistically no significant difference ($p = .79$; Table 4).

The distribution of 1-year OS and PFS was 96.6% and −97.5% in the BEAM arm and 95% and −95.1% in the Mx-Mel arm, respectively. The distribution of 5-year OS and PFS was 69% and −75% in the BEAM arm and 61% and −74% in the Mx-Mel arm. There was no statistically significant difference between the two subgroups ($p > .05$). The median duration of follow-up was 44 (range: 3−112) months and 14 (range: 3−62) months in the BEAM and Mx-Mel arms, respectively. It was observed to be significantly longer in the BEAM arm ($p < .001$; Table 4).

5. Discussion

The results of this study contain important findings in terms of comparing BEAM and Mx-Mel regimens and evaluating their efficacy in the lymphoma group. It contains very valuable data as it is based on single-center patients' results.

It is possible to say that there are similar studies in the literature which evaluate the effectiveness and toxicity of the BEAM regimen. In one of the important studies, Yeral et al. [17] retrospectively evaluated multicenter data of ASCT patients. In the study, in which the efficacy and toxicities of BEAM and Mx-Mel preparation regimens were discussed in detail, the 3-year expected OS and PFS after ASCT were 86.1% and 86.1% in the Mx-Mel group, respectively, while in the BEAM group it was 91.3% and 76.5%, respectively. Although febrile neutropenia attacks developed in 50% of the patients in the Mx-Mel group, this rate was 91.1% in the BEAM group. Grade II and higher hepatic, renal,

Table 3. Transplant, Engraftment and Toxicity Data of the Patients.

		All patients	BEAM	Mx-Mel	*p*
Patients (*n*)		**101**	**60**	**41**	
Mobilization regimen	Cisplatin-based + G-CSF	90	55 (91.7)	35 (85.4)	0.57
	Gemsitabin-based + G-CSF	4	2 (3.3)	3 (7.3)	
	Plerixifor + G-CSF	6	3 (5)	3 (7.3)	
CD34 × 10^6/kg	Median cell count	9 (4–12)	9 (4–11)	9 (5–12)	0.11
Neutrophil engraftment	Median days (min–max)	11 (9–20)	10 (9–20)	12 (9–19)	**<0.001**
Thrombocyte engraftment	Median days (min–max)	12 (9–21)	12 (9–21)	12 (10–21)	0.54
Febrile neutropenic attack		51 (50.5)	29 (48.3)	22 (53.6)	0.59
Fever of unknown origin		39	22 (36.7)	17 (41.5)	0.54
Proven infections		12	6 (10)	6 (14.6)	0.66
Bacteremia		6	3 (5)	3 (7.3)	
Pneumonia		2	1 (1.7)	1 (2.4)	
Gastrointestinal infection		2	1 (1.7)	1 (2.4)	
Urinary infections		2	1 (1.7)	1 (2.4)	
Mucositis	Grade I–II	37	22 (36.7)	15 (36.6)	0.95
	Grade III–IV	31	19 (31.7)	12 (29.3)	
Gastrointestinal toxicity	Grade I–II	35	22 (36.7)	13 (31.7)	0.83
	Grade III–IV	8	5 (8.3)	3 (7.3)	
Renal toxicity	Grade I–II	11	8 (13.3)	3 (7.3)	0.61
	Grade III–IV	2	1 (1.7)	1 (2.4)	
Hepatotoxicity	Grade I–II	10	6 (10)	4 (9.8)	0.70
	Grade III–IV	1	1 (1.7)	0	
Transplant-related 100-day mortality (%)	Transplant-related mortality (TRM)	3	2 (3.3)	1 (2.5)	0.79

Note. Data are presented as *n* (%) unless otherwise indicated. BEAM = BCNU, etoposide, ARA-C, and melphalan; G-CSF = granulocyte colony-stimulating factor; Mx-Mel = mitoxantrone–melphalan. Data bold in font: A p-value less than 0.05 (typically ≤ 0.05) is statistically significant.

gastrointestinal, and cardiac toxicity rates were similar in both groups. However, the pulmonary toxicity rate was 1.9% and 29.4% in the Mx-Mel and BEAM groups, respectively ($p < 0.001$). As a result of this study, the Mx-Mel preparation regimen appears to be as effective as the BEAM regimen but has better tolerability in terms of pulmonary toxicity and can be used as an alternative option if necessary, depending on the patient's comorbidity. In our study, gastrointestinal, hepatic, and renal toxicity was similar in both arms of regimens. We did not observe significant pulmonary toxicity in both groups. Similar results were obtained in both groups prepared for ASCT with similar demographic data. In contrast to this study, time to neutrophil engraftment was shorter in the BEAM arm; however, there is no statistical difference in terms of severe infectious complications and febrile neutropenic attacks. The evaluation of OS and PFS in the 1-year period of our study seems more optimal due to the significant difference in follow-up durations between the two groups. There was statistically no significant difference between 1-year OS and PFS between the two groups.

Okay et al. [11] reported the results of 53 patients who underwent ASCT with the Mx-Mel conditioning regimen in 14 patients with R/R HL and 39 patients with NHL. Of these, 44 (86.2%) patients achieved CR after peripheral stem cell infusion with this conditioning regimen. The 2-year estimated OS was 81.9% and PFS was 59.3%. In this mitoxantrone-based study, we see that an effective conditioning regimen has been put forward. Similarly, in another study conducted by Oyan et al. [18], efficacy was evaluated in ASCT cases performed with Mx-Mel conditioning regimen. In this Phase II study conducted with ASCT following the conditioning regimen in a total of 40 patients diagnosed with R/R

Table 4. The Survival and Follow-Up Data.

		Total patients	BEAM	Mx-Mel	*p*
1-year OS (%)		97	96.6	97.5	0.68
1-year PFS (%)		95	95	95.1	0.88
5-year OS (%)		69	69	75	0.70
5-year PFS (%)		63	61	74	0.81
Follow-up duration	Median months	24 (3–112)	44 (3–112)	14 (3–62)	**<0.001**

Note. BEAM = BCNU, etoposide, ARA-C, and melphalan; Mx-Mel = mitoxantrone–melphalan; OS = overall survival; PFS = progression-free survival.

HL and NHL; 35 (90%) of the patients achieved CR and the PFS rate was 71.7% at 4 years. TRM on Day + 100 was 2.5%. Similar to the 100-day TRM of this mitoxantrone-based study in which significant results were obtained with acceptable toxicity, mortality in our study was 2.9% with three patients. In another study conducted by Tarella et al. [19], effectiveness and hematologic/extrahematologic toxicities of the Mx-Mel regimen were examined. A total of 113 patients with lymphoma have undergone ASCT with Mx-Mel conditioning regimen and successful results have been obtained with effective treatment and reversible cardiotoxicity.

Engraftment failure, one of the most important transplant-related complications, was not observed in any of our cases; however, time to neutrophil engraftment was longer in the Mx-Mel group than in the other group. This result is parallel with the examples in the literature [17]. The point to be emphasized is that despite late neutrophil engraftment, significant infectious complications, febrile neutropenia attack, or TRM did not differ between the two groups. Despite the length of engraftment period, which can be considered as its most important disadvantage, the fact that the important infectious complications were not seen neither in our study, nor in the literature, makes the Mx-Mel regimen preferable and advantageous.

The search for an alternative to the BEAM regimen, which is considered the standard for lymphoma and ASCT, is based on carmustine toxicity. Several studies have attempted to substitute bendamustine thiotepa, fotemustine, lomustine, and mitoxantrone instead of carmustine to demonstrate high efficacy and low toxicity [11,17,19]. It can be said that alternatives are preferable to avoid late toxicities such as cardiovascular and pulmonary. There were no patients with significant pulmonary and cardiotoxicity in both our patient arms; however, due to retrospective examination, it was not possible to reach further examination results such as pulmonary function tests and echocardiography at predetermined intervals. Since there is no follow-up period to evaluate the development of secondary malignancy in our study and studies in the literature, the advantage in this area cannot be evaluated; however, it constitutes an important topic of discussion.

As reported in literature [19], the most important side effect associated with Mx-Mel is grade III–IV mucositis. In our study, 12 (29.3%) patients had grade III–IV mucositis; similarly, it is seen to be 31% in the literature [19]. While hepatotoxicity and increased liver enzymes were encountered in the same study at a rate of 9%, it was found to be 9.8% with four patients in our study. In this context, it can be said that the Mx-Mel regimen will constitute an alternative to BEAM regimen with low toxicity and similar efficiency.

There were also limitations of this study. The most important limitation was that patients were limited to a small group when divided into subgroups. Additionally, the fact that carmustine and its associated pulmonary and cardiac toxicities have not been analyzed is another important limitation point. The patients were evaluated retrospectively, and Mx-Mel/BEAM regimen was used according to treating physician's preference and it caused unpredictable difficulties in comparisons. At this point, a prospective study can be planned by dividing patients into subgroups according to certain conditions. Due to the significant difference in follow-up durations between the two groups, the evaluation does not appear to be optimal in terms of long-term OS and PFS.

In conclusion, with this study, we show that the Mx-Mel regimen has similar efficacy and toxicity compared with the BEAM regimen. Although time to neutrophil engraftment was shorter in the BEAM arm, it did not result as significant transplant-related complications between the two regimens. Contrary to the example in the literature, no difference was found in platelet engraftment. The Mx-Mel regimen is seen as a good alternative with low toxicity and high efficacy.

Ethics approval and consent to participate

Ethical committee approval was received (Approval date and number: 18.01.2019–1645) and the patients and control subjects gave informed consent before the beginning of the study. The experimental procedures were based on the Declaration of Helsinki and relevant institutional regulations.

Patient consent for publication

An informed consent obtained as written forms from all of our patients to publish.

Availability of data and materials

The authors declare that data supporting the findings of this study are available within the referenced articles.

Funding

No funding was received. None of the authors have disclosures relevant to this manuscript.

Authors' contributions

All authors contributed to the editing of the manuscript. IS wrote the manuscript and made tables.

Declaration of Competing Interest

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.

Acknowledgments

We respectfully remember all the colleagues we lost in the COVID-19 fight.

References

[1] Ansell SM. Hodgkin lymphoma: diagnosis and treatment. Mayo Clin Proc 2015;90:1574–83. https://doi.org/10.1016/j.mayocp.2015.07.005.
[2] Ansell SM. Hodgkin lymphoma: 2016 update on diagnosis, risk-stratification, and management. Am J Hematol 2016;91:434–42. https://doi.org/10.1002/ajh.24272.
[3] Shankland KR, Armitage JO, Hancock BW. Non-Hodgkin lymphoma. Lancet 2012;380:848–57. https://doi.org/10.1016/S0140-6736(12)60605-9.
[4] Zahid U, Akbar F, Amaraneni A, Husnain M, Chan O, Riaz IB, et al. A review of autologous stem cell transplantation in lymphoma. Curr Hematol Malig Rep. 2017;12:217–26. https://doi.org/10.1007/s11899-017-0382-1.
[5] Philip T, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapysensitive non-Hodgkin's lymphoma. N Engl J Med 1995;333:1540–5.
[6] Schmitz N, Pfistner B, Sextro M, Sieber M, Carella AM, Haenel M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. Lancet 2002;359:2065–71.
[7] Arakelyan N, Berthou C, Desablens B, de Guibert S, Delwail V, Moles MP, et al. Early versus late intensification for patients with high-risk Hodgkin lymphoma-3 cycles of intensive chemotherapy plus low-dose lymph node radiation therapy versus 4 cycles of combined doxorubicin, bleomycin, vinblastine, and dacarbazine plus myeloablative chemotherapy with autologous stem cell transplantation: five-year results of a randomized trial on behalf of the GOELAMS Group. Cancer 2008;113:3323–30.
[8] Robinson SP, Boumendil A, Finel H, Dreger P, Sureda A, Hermine O, et al. High-dose therapy with BEAC conditioning compared to BEAM conditioning prior to autologous stem cell transplantation for non-Hodgkin lymphoma: no differences in toxicity or outcome. A matched-control study of the EBMT-Lymphoma Working Party. Bone Marrow Transplant 2018;53:1553–9. https://doi.org/10.1038/s41409-018-0196-3.
[9] Singer S, Sharma N, Dean R, Zhao Q, Abounader D, Elder P, et al. BEAM or BUCYVP16-conditioning regimen for autologous stem-cell transplantation in non-Hodgkin's lymphomas. Bone Marrow Transplant 2019;54:1553–61. https://doi.org/10.1038/s41409-019-0463-y.
[10] Kim JE, Lee DH, Yoo C, Kim S, Kim SW, Lee JS, et al. BEAM or BuCyE high-dose chemotherapy followed by autologous stem cell transplantation in non-Hodgkin's lymphoma patients: a single center comparative analysis of efficacy and toxicity. Leuk Res 2011;35:183–7. https://doi.org/10.1016/j.leukres.2010.07.016.
[11] Okay M, Büyükaşõk Y, Demiroğlu H, Malkan ÜY, Çiftçiler R, Aladağ E, et al. Mitoxantrone-melphalan conditioning regimen for autologous stem cell transplantation in relapsed/refractory lymphoma. Turk J Med Sci 2019;49:985–92. https://doi.org/10.3906/sag-1809-36.
[12] Chen YB, Lane AA, Logan B, Zhu X, Akpek G, Aljurf M, et al. Impact of conditioning regimen on outcomes for patients with lymphoma undergoing high-dose therapy with autologous hematopoietic cell transplantation. Biol Blood Marrow Transplant 2015;21:1046–53. https://doi.org/10.1016/j.bbmt.2015.02.005.
[13] Sharma A, Kayal S, Iqbal S, Malik PS, Raina V. Comparison of BEAM vs. LEAM regimen in autologous transplant for lymphoma at AIIMS. Springerplus 2013;2:489.. https://doi.org/10.1186/2193-1801-2-489.
[14] Gilli S, Novak U, Taleghani BM, Baerlocher GM, Leibundgut K, Banz Y, et al. BeEAM conditioning with bendamustine-replacing BCNU before autologous transplantation is safe and effective in lymphoma patients. Ann Hematol 2017;96:421–9. https://doi.org/10.1007/s00277-016-2900-y.
[15] Olivieri J, Mosna F, Pelosini M, Fama A, Rattotti S, Giannoccaro M, et al. A comparison of the conditioning regimens BEAM and FEAM for autologous hematopoietic stem cell transplantation in lymphoma: an observational study on 1038 patients from Fondazione Italiana Linfomi. Biol Blood Marrow Transplant 2018;24:1814–22. https://doi.org/10.1016/j.bbmt.2018.05.018.
[16] Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol 1999;17:1244. https://doi.org/10.1200/JCO.1999.17.4.1244. Erratum in: J Clin Oncol 2000;18:2351.
[17] Yeral M, Aytan P, Gungor B, Boga C, Unal A, Koc Y, et al. A comparison of the BEAM and MITO/MEL conditioning regimens for autologous hematopoietic stem cell transplantation in hodgkin lymphoma: an analysis of efficiency and treatment-related toxicity. Clin Lymphoma Myeloma Leuk 2020;20:652–60. https://doi.org/10.1016/j.clml.2020.05.009.
[18] Oyan B, Koc Y, Ozdemir E, Kars A, Turker A, Tekuzman G, et al. High dose sequential chemotherapy and autologous stem cell transplantation in patients with relapsed/refractory lymphoma. Leuk Lymphoma 2006;47:1545–52. https://doi.org/10.1080/10428190600570958.
[19] Tarella C, Zallio F, Caracciolo D, Cuttica A, Corradini P, Gavarotti P, et al. High-dose mitoxantrone + melphalan (MITO/L-PAM) as conditioning regimen supported by peripheral blood progenitor cell (PBPC) autograft in 113 lymphoma patients: high tolerability with reversible cardiotoxicity. Leukemia 2001;15:256–63. https://doi.org/10.1038/sj.leu.2402011.