Original Article

A Comparison of the BEAM and BuCyE Conditioning Regimens for Autologous Stem Cell Transplantation in Lymphoma: A Single-Center Experience

Lenfomada Otolog Kök Hücre Transplantasyonu için BEAM ve BuCyE Hazırlama Rejimlerinin Karşılaştırması: Tek Merkez Deneyimi

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ABSTRACT

Introduction: High-dose chemotherapy together with autologous stem cell transplantation (ASCT) is a commonly used treatment modality in patients with relapsed/refractory Hodgkin's lymphoma (HL) or non-Hodgkin's lymphoma (NHL). The aim of this study was to investigate the efficacy and toxicity of BuCyE (busulfan, cyclophosphamide, and etoposide) and BEAM (carmustine, etoposide, cytarabine, and melphalan) conditioning regimens in patients with relapsed/refractory lymphoma scheduled for ASCT.

Methods: Between December 2018 and November 2019, 24 patients with relapsed or refractory HL (n=16) and NHL (n=8) who underwent ASCT following BEAM (n=12) and BuCyE (n=12) preparative regimens were analyzed retrospectively at Bone Marrow Transplantation Unit of Abdurrahman Yurtaslan Ankara Oncology Training and Research. The groups were compared in terms of patient characteristics, hematopoietic engraftment time, toxicity profiles, and progression free survival (PFS).

Results: No significant differences were detected between the groups with regard to age, gender distribution, ecog, sorror score, diagnosis, pre-ASCT stage (early/late), chemotherapy line, pre-ASCT response and pre-ASCT radiotherapy ($p>0.05$). The median number of infused CD34+ cells/kg, neutrophil and platelet engraftment statuses, duration of hospitalization, need for erythrocyte and platelet transfusion of BuCyE and BEAM groups were found to be similar ($p>0.05$). More patients in the BuCyE group developed mucositis and febrile neutropenia, but this difference was not statistically significant ($p>0.05$). At a median follow-up of 13 months(1–21 months) after ASCT, the median PFS could not be reached. No difference was found in PFS between regimes ($p = 0.68$).

Discussion and Conclusion: BuCyE followed by ASCT is an effective conditioning regimen in relapsed/refractory lymphoma patients. This regimen may be an important treatment option as a substitute for carmustine containing regimens. However, in the absence of prospective trials, it is difficult to suggest a conditioning regimen due to the low level of evidence. It is important to participate in ongoing clinical trials.

Keywords: Lymphoma, autologous stem cell transplantation, BuCyE, BEAM

ÖZET

Giriş ve Amaç: Otolog kök hücre transplantasyonu (OKHN) ile birlikte uygulanan yüksek doz kemoterapi, relaps/refrakter Hodgkin lenfoma (HL) veya Hodgkin dışı lenfoma (NHL) olan hastalarda yaygın olarak kullanılan bir tedavi yöntemidir. Bu çalışmanın amacı, OKHN planlanan relaps/refrakter lenfomalı hastalarda BuCyE (busulfan, siklofosfamid ve etoposit) ve BEAM (karmustin, etoposit, sitarabin ve melfalan) hazırlama rejimlerinin etkililiğini ve toksisitesini araştırmaktır.

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Yöntem ve Gereçler: Aralık 2018 ile Kasım 2019 arasında BEAM (n=12) ve BuCyE (n=12) hazırlık rejimleri ile OKHN yapılan nükseden veya dirençli HL (n=16) ve NHL (n=8) olan 24 hasta, Abdurrahman Yurtaslan Ankara Onkoloji Eğitim ve Araştırma Kemik İliği Nakli Ünitesi'nde incelendi. Gruplar hasta özellikleri, hematopoietik engraftman süresi, toksisite profilleri ve progresyonsuz sağkalım (PFS) açısından karşılaştırıldı.
Bulgular: Gruplar arasında yaş, cinsiyet dağılımı, ecog, sorror skoru, tanı, OKHN öncesi evre (erken/geç), kemoterapi sayısı, OKHN öncesi yanıt ve OKHN öncesi radyoterapi açısından anlamlı farklılık saptanmadı (p>0.05). BuCyE ve BEAM gruplarının ortalama infüze edilen CD34+ hücre/kg sayısı, nötrofil ve trombosit engraftman durumları, hastanede kalış süreleri, eritrosit ihtiyacı ve trombosit transfüzyonu benzer bulundu (p>0.05). BuCyE grubunda daha fazla hastada mukozit ve nötropenik ateş gelişti, ancak bu fark istatistiksel olarak anlamlı değildi (p>0.05). OKHN'den sonraki 13 aylık (1–21 ay) medyan takipte, medyan PFS'ye ulaşılamadı. Rejimler arasında PFS'de fark bulunmadı (p=0.68).
Tartışma ve Sonuç: BuCyE'yi takiben OKHN, relaps/refrakter lenfoma hastalarında etkili bir hazırlık rejimidir. Bu rejim, karmustin içeren rejimlerin yerine geçebilecek önemli bir tedavi seçeneği olabilir. Bununla birlikte, ileriye dönük çalışmaların yokluğunda, düşük düzeyde kanıt nedeniyle bir hazırlama rejimi önermek zordur. Devam eden klinik araştırmalara katılmak önemlidir.

Anahtar Kelimeler: Lenfoma, otolog kök hücre nakli, BuCyE, BEAM

Introduction

Most patients with Hodgkin lymphoma (HL) are cured with initial therapy. However, 5-10 % of the patients have a treatment-refractory disease and 10-30% will relapse following standard therapy. Although significant advances have been achieved in the treatment of non-Hodgkin's lymphoma (NHL), 40–60% of the patients still relapse or have a treatment-refractory disease [1].

Many randomized studies have shown significant improvements in progression-free survival (PFS) and event-free survival (EFS) with high-dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT) in relapsed/refractory HL and NHL [1–3].

The most commonly used high-dose conditioning regimens in relapsed/refractory HL and NHL patients are BEAM (carmustine, etoposide, cytarabine, and melphalan), BEAC (carmustine, etoposide, cytarabine, and cyclophosphamide), CBV (cyclophosphamide, carmustine, etoposide), BuCyE (busulfan, cyclophosphamide, etoposide) and combination regimen with total body irradiation. BEAM is the most commonly preferred HDC regimen among these [4, 5]. The number of randomized studies comparing these regimens to date is quite low. Advances in conditioning regimens and supportive therapy have resulted in a reduction in transplant-related mortality. Although the search for a different regimen continues, recent supply and cost issues for carmustine have created an urgent need for alternative conditioning regimens [6].

The aim of this study was to investigate the efficacy and toxicity of BuCyE and BEAM conditioning regimens in patients with relapsed/refractory HL or NHL scheduled for ASCT.

Materials and methods

In this study, relapsed or refractory NHL or HL patients who received ASCT after salvage chemotherapy at Abdurrahman Yurtaslan Ankara Oncology Education and Research Bone Marrow Transplantation Unit between December 2018 and November 2019 were retrospectively analyzed. The patients with relapsed or refractory NHL and HL who had been diagnosed histopathologically were

Table 1. BuCyE and BEAM chemotherapy regimens

BuCyE protocol		BEAM protocol	
Busulfan (mg/kg)	16 (-7, -6, -5, -4. days)	Carmustine (mg/m^2)	200 (-7. day)
Cyclophosphamide (mg/kg)	120 (-3, -2. days)	Etoposide (mg/m^2)	200 (-6, -5, -4, -3. days)
Etoposide (mg/m^2)	400 (-3, -2. days)	Cytarabine (mg/m^2)	200 (-5, -4, -3, -2. days)
		Melphalan (mg/m^2)	140 (-2. day)

Table 2. Patient characteristics of all patients (n = 24)

Parameters	BEAM (n = 12)	BuCyE (n = 12)	P value
Age (median)	40 (20-59)	36,5 (27-65)	0,51
Gender (M/F)	9/3	10/2	1
ECOG (0/1)	5/7	4/8	1
Sorror Score (0/1-2)	10/2	11/1	0,6
Diagnosis (HL/NHL)	8/4	8/4	1
Disease type			
HL			
NS	5	5	
MC	2	2	
LR	1	-	
LD	-	1	
NHL			
DLBCL	3	3	
BL	1	1	
Pre-ASCT Disease Stage (I-II/ III-IV)	4/8	2/10	0,64
Chemotherapy Line (1-2/ ≥3)	7/5	5/7	0,41
Pre-ASCT Response (CR-PR/Progresyon)	11/1	11/1	1
RT (yes/no)	2/10	2/10	1

M: Male, F: Female, HL: Hodgkin's lymphoma, NS:Nodular Sclerosis , MC: Mixed Cellularity, LR: Lymphocyte Rich, LD: Lymphocyte Depleted, NHL: Non-Hodgkin's lymphoma, DLBCL: Diffuse large B cell lymphoma, BL: Burkitt lymphoma, ASCT: Autologous stem cell transplantation, CR: Complete remission, PR: Partial remission, RT: Radiotherapy.

accepted as suitable candidates for ASCT. All cases enrolled in the study were assessed in terms of chemosensitivity. The other inclusion criteria of the study were age <70 years, adequate heart, lung, liver, and kidney reserves, sufficient hematopoietic function, and Eastern Cooperative Oncology Group performance status of one or zero prior to ASCT. The study involved a total number of 24 patients with lymphoma scheduled for ASCT. Among these patients, 12 cases received BuCyE regimen, while BEAM was applied to 12 patients as preparative regimen prior to ASCT (Table 1). Successful neutrophil engraftment was accepted as an absolute neutrophil count of $\geq 1\times10^9$/L attained for one day, while platelet count $\geq 20\times10^9$/L without a need for platelet transfusion on the first consecutive three days after platelet engraftment was considered to be a successful platelet engraftment procedure. Treatment response was first evaluated one month after ASCT performed, then by 3-months intervals within the first 2 years. The groups were compared in terms of patient characteristics, hematopoietic engraftment time, toxicity profiles, and PFS. PFS was calculated as the time between the day of ASCT and data collection or exitus.

Table 3. Hospitalization process and findings after ASCT

Parameters	BEAM (n =12)	BuCyE (n = 12)	P value
Duration of diagnosis to ASCT (months) (median)	21 (4-214)	27,1 (9-91)	0,41
Diagnosis to transplant > = 24 months HL/NHL	4/1	7/1	
Diagnosis to transplant < 24 months HL/NHL	4/3	1/3	
Duration of Hospitalization (days)	22 (19-26)	22,5 (19-35)	0,29
Infused CD34 kg/cell (median)	9,8 (4,7-14)	6,59 (3,1-16,3)	0,14
Neutrophil engraftment (days) (median)	10(8-10)	10 (9-17)	0,09
HL (median)	10 (8-10)	10 (9-17)	
NHL (median)	10 (8-10)	10 (9-12)	
Platelet engraftment (days) (median)	11 (6-19)	10 (9-32)	0,35
HL (median)	12 (9-19)	10 (9-26)	
NHL (median)	10 (6-12)	12 (9-32)	
Need of ES transfusion(yes/no)	6/6	5/7	0,68
HL patients given ES transfusion	2	5	
NHL patients given ES transfusion	4	-	
Need of PLT transfusion (1-2/ ≥3)	8/4	6/6	0,4
HL patients given PLT transfusion (1-2/ ≥3)	4/4	4/4	
NHL patients given PLT transfusion (1-2/ ≥3)	4/-	2/2	
Mucositis (yes/no)	0/12	3/9	0,22
HL patients with mucositis	-	1	
NHL patients with mucositis	-	2	
Febrile Neutropenia (yes/no)	7/5	8/4	0,67
HL patients with febrile neutropenia	3	7	
NHL patients with febrile neutropenia	4	1	

ASCT: Autologous stem cell transplantation, HL: Hodgkin's lymphoma, NHL: Non-Hodgkin's lymphoma, ES: Erythrocyte suspension, PLT: Platelet.

Statistical analysis

Statistical analyses were performed with IBM SPSS (Version 26) software. Demographical data were summarized with descriptive statistics. Numerical variables were presented as median (minimum-maximum), categorical variables were presented as ratios. To compare groups, Mann Whitney U tests were used for numerical variables and Chi-square test was used for categorical variables. Kaplan-Meier survival analysis performed for PFS and log-rank test was applied to assess survival difference among groups. $P \leq 0.05$ was regarded as statistically significant.

Results

The median age of the patients was 38 (20-65). Of the patients, 33.3% had NHL and 66.7 % had HL. There were 19 (79.2%) male patients and 5 (20.8%) female patients. The median time between diagnosis and ASCT was 21 months (4-214) and 27.1 months (9-91) in BEAM and BuCyE groups, respectively. The characteristics of all patients are included in Table 2.

No significant differences were detected between the groups with regard to age, gender distribution, ecog, sorror score, diagnosis, pre-ASCT stage (early/late), chemotherapy line, pre-ASCT response and pre-ASCT radiotherapy ($p>0.05$) (Table 2). Median number of infused CD34+ cells/kg, neutrophil and platelet engraftment statuses, duration of hospitalization, need for erythrocyte and platelet transfusion of BuCyE and BEAM groups were found to be similar ($p>0.05$). More patients in the BuCyE group developed mucositis and febrile neutropenia, but this difference was not statistically significant ($p>0.05$) (Table 3).

At a median follow-up of 13 months (1–21 months) after ASCT, the median PFS could not be reached, and no difference was determined in PFS between the regimes ($p = 0.68$) (Figure 1).

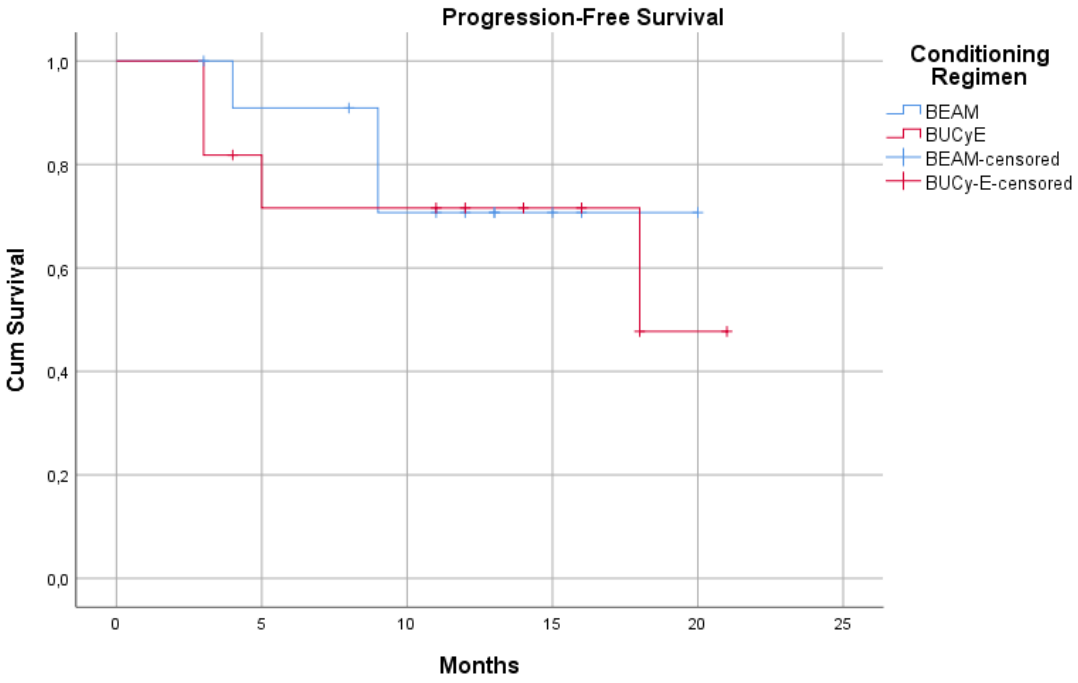

Figure 1. At a median follow-up of 13 months (1–21 months) after ASCT, the median PFS could not be reached and no difference was obtained in PFS between the regimes (p = 0.68).

Discussion

Despite the advances in modern chemotherapy, a significant proportion of patients with NHL or HL either never achieve remission or relapse early. For the vast majority of these patients, HDC followed by ASCT remains the best option for a long-lasting complete response. The most popular conditioning protocol for ASCT in lymphoma is BEAM.

Recent supply and cost issues, the high rate of mucositis requiring parenteral nutrition, and the high incidence of chronic interstitial pulmonary fibrosis for carmustine have created an urgent need for alternative conditioning regimens [6].

The resulting cost of carmustine, both drug-related and of managing toxicities, have spurred the development of novel regimens that replace this agent.

In several studies, bendamustine, thiotepa, fotemustine, lomustine, and mitoxantrone, have been examined as substitutions for carmustine in the BEAM regimen, resulting in similar or superior efficacy with a reduction in toxicity [7-10].

However, the lack of randomized trials using these agents and the fact that they include different study populations with differing proportions of histologies make it difficult to compare across studies.

Hanel M et al. conducted a study on 53 patients with HL or NHL who received high dose BuCyE conditioning regimen and investigated the efficacy and toxicity of BuCyE used as a preparative regimen prior to ASCT. In the evaluation of toxicities, mucositis (79%) and hepatic toxicity (15%) were found to be the most common non-hematological toxicities which were seen in 52 subjects, while three patients (5.8%) experienced severe veno-occlusive disease. In that study, the rate of treatment-related mortality was found as 3.8%. The authors concluded that BuCyE was an effective and well-tolerated conditioning regimen in patients with HL and NHL [5]. In our study,

none of the patients had veno-occlusive disease and in the BuCyE group, the rate of mucositis was 25% (n=3/12) and treatment-related mortality was not.

Singer S. et al. [11] retrospectively compared the BEAM and BuCyE for patients with relapsed NHL undergoing AHCT. After a median follow-up of 3.9 years for BEAM and 4.3 years for BuCyE from AHCT, PFS was found similar between the two conditioning regimens. In this study; it was reported that the number of CD34 infused was higher in the BuCyE group, the platelet engraftment time and hospital duration was shorter than in the BEAM group. In terms of adverse effects, mucositis was significantly more common in the BuCyE group, whereas sinusoidal obstruction syndrome was more common in the BEAM group.

Singer S. et al. [12] retrospectively compared the BEAM and BuCyE for patients with relapsed HL undergoing AHCT. They reported that the use of BEAM conditioning before AHSCT resulted in a statistically significant PFS, OS and lower relapse compared to BuCyE. In this study; it was reported that the number of CD34 infused was higher in the BuCyE group and the platelet engraftment time was shorter than in the BEAM group. They found the length of hospital stay was significantly shorter for the BEAM group and overall toxicities did not differ significantly between the two groups except for high rates of mucositis with BuCyE.

Berber et al. [13] compared 31 patients who received BuCyE and 11 patients who received BEAM in their study. No difference was obtained between the groups as regards the neutrophil and platelet engraftment duration and need for erythrocyte and platelet suspension during the transplantation. Also, mucositis, nausea, vomiting, diarrhea, infectious complications, and transplant-related mortality were found as similar. No statistically significant difference was determined between the groups as regards post-transplantation survival, total survival and EFS rates. As a result, BuCyE and BEAM were found as similar in terms of toxicity profile, and it was maintained that BuCyE could be an alternative preparation regimen. In our study, no difference was determined between both groups in terms of hospitalization duration, neutrophil and platelet engraftment duration, need for erythrocyte and platelet suspension, mucositis and febrile neutropenia, and thus it is similar to the study by Berber et al as regards the results.

In their study, Gunduz et al. [14] reported that in the patients given a BEAM (n=10) and BuCyE (n=10) preparation regimen, neutrophil and platelet engraftment duration, 100^{th} day remission state, hospitalization period, post-transplantation relapse and death, and need for total erythrocyte and platelet suspension were similar in both groups, but survival period is longer in the group receiving BEAM (55.25±15.29 vs. 12.12±4.02 months, $p = 0.02$). In our study, adverse effect profile, support treatment and hospitalization period were similar, and no difference was determined in PFS.

As a result, a small number of patients and a short follow-up time are insufficient to derive firm conclusions. However, a BuCyE conditioning regimen prior to ASCT was a well-tolerated and effective treatment for relapsed/refractory NHL and HL. This regimen may be an important treatment option as a substitute for carmustine containing regimens. Since, carmustine supply and cost issues urge for a search for alternative conditioning regimens.

However, in the absence of prospective trials, it is difficult to suggest a conditioning regimen due to the low level of evidence. It is important to participate in ongoing clinical trials.

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