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Evaluation of busulfan, cyclophosphamide, and etoposide as a preparation regimen for autologous stem cell transplantation in Hodgkin's lymphoma patients

Soykan Biçim, Mehmet Ali Erkurt, İrfan Kuku, Emin Kaya, İlhami Berber, Ahmet Kaya, Emine Hidayet[1], Ayşe Uysal[2], Ahmet Sarıcı[3], İlknur Nizam Özen[4]

Department of Hematology, Turgut Ozal Medical Center, Inonu University, [3]Division of Hematology, Malatya Education and Research Hospital, Malatya, [1]Department of Hematology and Bone Marrow Transplantation Center, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, [2]Department of Hematology, Faculty of Medicine, Fırat University, Elazığ, [4]Department of Hematology, Antalya Education and Research Hospital, Antalya, Turkey

Address for correspondence:
Dr. Mehmet Ali Erkurt, Department of Hematology, Turgut Ozal Medical Center, Inonu University, Malatya, Turkey.
E-mail: erkurtali@hotmail.com

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Abstract:

BACKGROUND: Hodgkin's lymphoma (HL) exhibits a cure rate of 90% in patients diagnosed at an early stage and a cure rate ranging from 70% to 90% in patients diagnosed at an advanced stage. In the case of patients with relapsed/refractory HL (r/rHL), it is recommended to provide salvage chemotherapy initially, followed by autologous stem cell transplantation (ASCT). The ideal conditioning regimen for the transplantation process is still being investigated.

OBJECTIVES: For individuals with r/rHL, high-dose chemotherapy combined with ASCT (HD-ASCT) is thought to be the most effective method of treatment. The purpose of this research was to evaluate the effectiveness and safety of the busulfan, cyclophosphamide, and etoposide (BuCyE) preparation regimen in r/rHL patients.

MATERIALS AND METHODS: Retrospective analysis was conducted on the data of 67 lymphoma patients older than 18 years who had HD-ASCT with the BuCyE conditioning regimen between September 2014 and November 2021 (86 months). The research consisted of 34 r/r HL patients among them. A parenteral regimen of 0.8 mg/kg of busulfan every 6 h from day −7 to day −5, 50 mg/kg of cyclophosphamide on days −3 and −2, and 400 mg/m^2 of etoposide on days −5 and −4 comprised the patient preparation regimen before ASCT. All data were collected from inpatient files and the Inonu University Turgut Ozal Medical Center Hospital Information System.

RESULTS: The median age of the patients was 43 years, and 67.6% were males. The most common type of HL was nodular sclerosis, which was followed by mixed cellularity. The median time for platelet and neutrophil engraftment was 14 and 11 days, respectively. 5.0 × 10^6/kg was the median transplanted dose of CD34+ cells (2.1–13.55). Liver toxicity was observed in 6 (17.6%) patients. Eight patients suffered from pulmonary side effects. The median number of previous chemotherapies was 2 (2–4). In all lymphoma patients, the complete response rate was 61.8% (n = 21), whereas the disease progression rate was 32.3% (n = 11). Transplantation-related mortality on the 100th day was 8.8% (n = 3). Three-year overall survival was 57.17%.

CONCLUSION: When the literature was reviewed, the studies with the BuCyE preparation regimen in patients with r/rHL were limited. This conditioning regimen was found to have fewer side effects and a lower cost. It can be preferable when compared to carmustine (BCNU), etoposide, cytarabine (ARA-C), and melphalan (known as BEAM) in r/rHL.

Keywords:

Busulfan, cyclophosphamide, etoposide, Hodgkin's lymphoma, stem cell transplantation

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Introduction

Hodgkin's lymphoma (HL) is thought to be a treatable hematological cancer. With chemotherapy and monoclonal antibody-based treatments, we currently have a cure rate of 90% in early-stage disease and 70%–90% in advanced-stage patients. Salvage chemotherapy followed by autologous stem cell transplantation (ASCT) is recommended for individuals with relapsed/refractory HL (r/rHL). Despite this intensive therapy, the disease progresses in approximately 50% of patients.[1]

The main component of conventional care for individuals with r/r HL is ASCT. Two important clinical trials, the British National Lymphoma Investigation in 1993[2] and the joint German Hodgkin Study Group trial in 2002,[3] compared high-dose chemotherapy with ASCT (HD-ASCT) versus chemotherapy and demonstrated significant benefits of ASCT. It includes high myeloablative drugs, so it is difficult to choose the optimal preparative regimen. The optimal regimen should include few side effects, a good overall and progression-free survival rate, and brief hospitalization, neutropenia, and thrombocytopenia periods.

A lot of drug combinations are used for the best preparation for transplantation. Cyclophosphamide (Cy), etoposide (E), melphalan, cytarabine, thiotepa, carmustine, busulfan (Bu), or total body irradiation-based regimens are commonly used for stem cell transplantation (SCT).[4] When busulfan based is detailed, it is difficult to say effective and harmless dosage. In addition to the difficulty of choosing the right dose, the oral delivery of high-dose Bu during stem cell transplant preparation regimens has a significant risk of fatal hepatic or pulmonary damage because of unintentional overdosing.[5] The goal of this research is to assess the parenteral busulfan, cyclophosphamide, and etoposide (BuCyE) combination's efficacy, adverse effects, and survival rates in HL patients undergoing ASCT.

Materials and Methods

The data of 67 lymphoma patients who were older than 18 years and underwent HD-ASCT with the BuCyE conditioning regimen between September 2014 and November 2021 (86 months) were examined retrospectively. The research consisted of 34 r/r HL patients among them. Patients with non-Hodgkin and other B-cell lymphomas were not included to reduce study heterogeneity. All data were collected from inpatient files and the Inonu University Turgut Ozal Medical Center Hospital Information System. HD-ASCT was performed with the informed permission of all patients.

Hematopoietic stem cells were obtained from peripheral blood. Single-agent granulocyte colony-stimulating factor (n = 33, 97%) and chemotherapy combined with the granulocyte colony-stimulating factor (n = 1, 3%) were the methods of mobilization. The median dose of $CD34^+$ cells administered was 5.0×10^6/kg (2.1–13.55). A large diameter (12F × 8'') central venous catheter was used to collect the hematopoietic stem cells.

The viral serology (hepatitis, HIV, cytomegalovirus, and Epstein–Barr virus), liver, and renal functions of all patients were measured before the chemotherapy. Antiviral (valacyclovir 500 mg/day), antibacterial (moxifloxacin 400 mg/day and trimethoprim–sulfamethoxazole 800/160 mg q 12 h [2 days in a week]), and antifungal (fluconazole 200 mg q 12 h) prophylaxis was given to all patients. Antiepileptic prophylaxis with phenytoin was given at a dosage of 10 mg/kg on day −8. It was administered as a load dose one day before the first dose of Bu, followed by 100 mg every 8 hours for 5 days. The phenytoin levels in the serum could not be measured. Mesna 75 mg/kg/day was infused for 24 h on days −2 and −3 against hemorrhagic cystitis caused by Cy.

The patient preparation regimen before ASCT included parenteral forms of busulfan (0.8 mg/kg q 6 h from day −7 to −5), cyclophosphamide (50 mg/kg on days −3 and −2), and etoposide (400 mg/m^2 on days −5 and −4). The chemotherapy dosages were calculated based on either the actual or ideal body weight, whichever was smaller.

The 1st day of 3 days that the absolute neutrophil count was >500 × 10^6/mL or the 1st day that it was >1000 × 10^6/mL in the absence of any support was considered myeloid engraftment. The 1st day of 3 days that the platelet count surpassed 20,000 × 10^6/mL or the 1st day that it exceeded 50,000 × 10^6/mL without a transfusion was considered platelet engraftment. The patient's response was assessed after 1 month following the ASCT. Transplant-related mortality refers to death occurring in the first hundred days after transplantation for which no other cause could be found. Liver toxicity was described as an elevation of serum transaminase and bilirubin levels (3 times the upper level of normal) without any explainable situation (e.g., reactivation of hepatitis or obstructive jaundice). Pulmonary toxicity was defined as a drop in saturation below 90%, which requires oxygen support for a minimum of 1 day and pulmonologist consultation (pulmonary emboli and infective causes of pneumonia were excluded from the study). Overall survival (OS) was achieved between the day of hematopoietic SCT and the date of death or last follow-up. A significant portion of the patients included in the study came from other cities. After a while after the

transplant, they continued their follow-up in hospitals close to their hometown. For this reason, a shortcoming of our study was that progression-free survival could not be determined. The Kaplan–Meier method was used to create the survival curves, and the statistical data (median OS and 3-year OS) were collected using the SPSS software program (SPSS 21.0 Inc., Chicago, IL, USA). The Inonu University Non-Interventional Research Ethics Committee gave permission to the study on March 29, 2022, with approval number 2022/3179.

Results

This retrospective analysis comprised 34 HL patients who were cured with ASCT at the Inonu University Turgut Ozal Medical Center. The median age of patients was 43 (range: 20–79) years, and 23 (67.6%) patients were male [Table 1]. Nodular sclerosis was the most frequent histological subtype of HL ($n = 15$, 44.2%). Other common subtypes included mixed cellularity (n = 7, 20.6%), lymphocyte predominant (n = 6, 17.6%), not otherwise described (n = 5, 14.7%), and lymphocyte depleted ($n = 1$, 2.9%). The median platelet engraftment time was 14 (8–43), and neutrophil engraftment was 11 (8–35) days after transplantation. 5.0×10^6/kg was the median transplanted dose of CD34+ cells (2.1–13.55). Liver toxicity was observed in 6 (17.6%) patients. Eight patients suffered from pulmonary side effects. One of them influenced both negative impacts. Renal insufficiency was determined in two patients. Febrile neutropenia and oral mucositis were seen in 20 patients. The median number of previous chemotherapies was 2 (2–4). Posttransplantation complete response (CR) was 61.8% (n = 21), and progression of disease was 32.3% ($n = 11$). Transplantation-related mortality on the 100^{th} day was 8.8% ($n = 3$). Two patients died from cardiac causes, and one patient died from septic causes. One patient did not reach the 30^{th} day of posttransplantation. Three-year OS was 57.17% [Figure 1], and the median OS was 23 months. It determined that 3-year OS was

Table 1: Patient features and transplant results

Variable	*N* (range or %)		
Number of patients (*n*)	34		
Age (years), median (range)	43 (20–79)		
Gender, *n* (%)			
Male	23 (67.6)		
Female	11 (32.4)		
Histology of Hodgkin's lymphoma, *n* (%)			
Nodular sclerosis	15 (44.2)		
Mixed cellularity	7 (20.6)		
Lymphocyte depleted	1 (2.9)		
Lymphocyte predominant	6 (17.6)		
NOS	5 (14.7)		
Number of prior chemotherapy regimens (%)			
2	26 (76.5)		
3	7 (20.6)		
4	1 (2.9)		
Disease response after transplantation, *n* (%)			
Complete remission	21 (61.8)		
Partial remission	2 (5.9)		
Progression	11 (32.3)		
Transplanted cell count, median (range)			
CD34+ cells	5.0×10^6 (2.1–13.55)		
Engraftment time, days (range)			
Neutrophil engraftment time	11 (8–35)		
Platelet engraftment time	14 (8–43)		
Causes of death (in the first 100 days), *n* (%)			
Cardiac	2		
Sepsis	1		
Toxicity and side effects	**Grade 3, *n* (%)**	**Grade 4, *n* (%)**	**Total of grade ≥3, *n* (%)**
Liver	6 (17.6)	0	6 (17.6)
Pulmonary	7 (20.6)	1 (2.9)	8 (23.5)
Renal	2 (5.8)	0	2 (5.8)
Febrile neutropenia	18 (52.9)	2 (5.8)	20 (58.7)
Oral mucositis	20 (58.8)	0	20 (58.7)

NOS=Not otherwise specified

ranked as lymphocyte predominant (80%), nodular sclerosis (63.82%), not otherwise specified (60%), mixed cellularity (25.7%), and lymphocyte-depleted type [Figure 2]. One patient could not reach the neutrophil and platelet engraftment and had cardiac mortality.

Discussion

r/rHLs have a high rate of mortality.[1] ASCT is a recommended therapy opinion for these disease conditions. There are different preparations of chemotherapy regimens in ASCT, different doses, and administration routes (oral, parenteral, and pharmacokinetics [Pk]-directed dose adjustment). This single-center, retrospective study showed that BuCyE is an alternative, effective, and economic combination (e.g., carmustine-based regimens are 10 times more expensive in Turkey) for ASCT in HL. Nevertheless, this preparative chemotherapy regimen includes some risks about mortality and morbidity, such as liver and pulmonary toxicities. When we look at the literature, it is evident that studies with the BuCyE preparation regimen in patients with HL were limited.

Carmustine-based regimens are frequently used to condition ASCT. For example, carmustine, E, cytarabine, Cy, and mesna (BEAM) were used for many years and had a 5-year OS of 53% only with non-HL (NHL) patients, respectively.[6] A 2-year OS rate of 83.9% was reported by Olivieri *et al*., with an overall response status of 91% at day 100 post-ASCT with BEAM. Twenty-seven percent of all patients had HL (n = 64), and 57% of them had aggressive NHL in this study design. Lung comorbidity was similar to our study, but 8.5% of them were severe with BEAM. Less liver toxicity was seen with BEAM (only 2% of all patients). Neutrophil engraftment day was the same as BuCyE, but platelet engraftment was reached 2 days earlier with BEAM.[7]

In a different comparison research, mucositis and febrile neutropenia were more common with the BuCyE preparation regimen. The neutrophil and platelet engraftment times, length of hospital stay, and need for transfusion were detected similar in both experiments.[8] Compared to the data in our study, febrile neutropenia was similar and oral mucositis was detected less frequently in this study of 12 patients.

According to a study with NHL patients, total body irradiation with added cyclophosphamide and etoposide showed a 3-year disease-free survival rate of 57% without Bu.[9] When melphalan was added to the Bu and E combination (BUEM), the 3-month OS was found to be 93.8%. However, with this addition, the platelet engraftment was delayed to the 17th day, and a significant change in neutrophil engraftment day (the 11th day) was not detected. It was observed that the transplant-related mortality outcomes of the BUEM regimen were close to BuCyE (6.25% vs. 8.8%).[4]

A 5-year cumulative incidence of 29% relapse with BEAM was reported by Singer *et al*. It is compared with another Bu-, Cy-, and E-included regimen (called BUCYVP16 in this study, and etoposide was given 40 mg/kg on days −5 to −4, and cyclophosphamide was given 60 mg/kg on days −3 to −2), and the relapse rate was 56% of all HL patients. OS was not achieved with BEAM but was 7.8 years with BUCYVP16. When compared to BUCYVP16, the BEAM conditioning regimen resulted in a reduced relapse and a superior OS in this research. This supports the use of BEAM as a preparative regimen before ASCT for early relapsed and non-CR HL, although

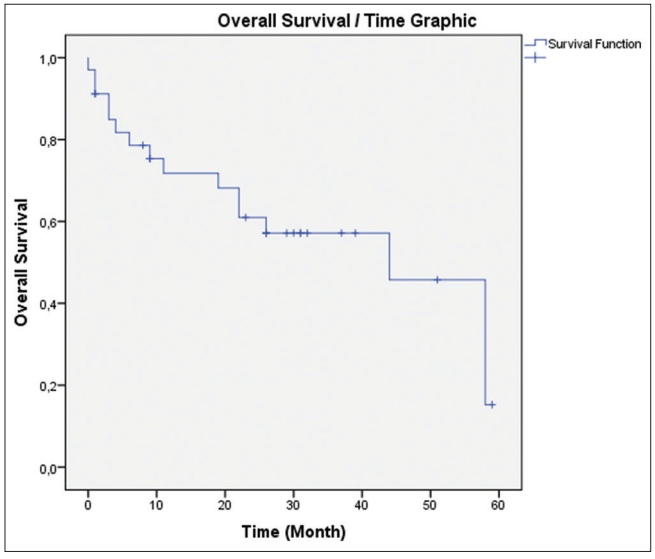

Figure 1: Overall survival in Hodgkin's lymphoma patients

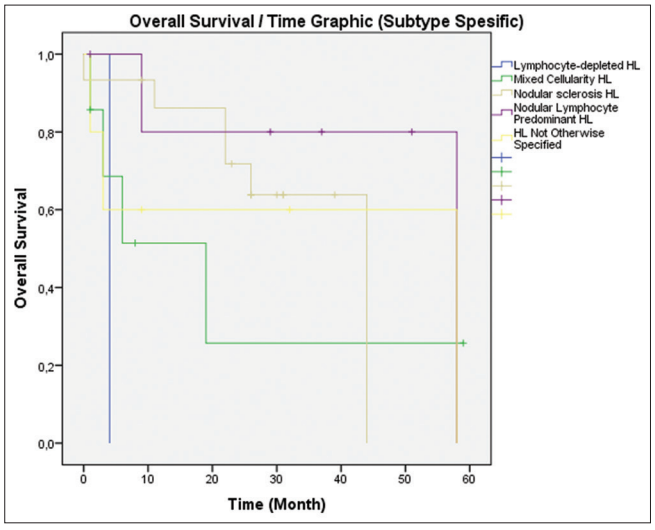

Figure 2: Overall survival in Hodgkin's lymphoma patients (subtype specific)

further research is needed.[10] Although there is more experience in NHL in general, that is not enough for HL.

Pasquini *et al*. found a 2-year OS of 76% for all patients who prepared with Bu, Cy, and E. This value was found 62% in our study, respectively. This difference may have resulted from the patient pool. One out of three patients had Hodgkin; the other one had diffuse large B-cell lymphoma (DLBCL) in this study. BuCyE was also linked to faster disease development and lower progression-free survival as compared to BEAM conditioning. However, treatment-related mortality and OS did not suffer by either BEAM or BuCyE regimen.[11]

Therefore, another study made in Brazil showed similar safety profiles and survival rates in both BEAM and BuCyE conditioning regimens. BuCyE preparative regimen can be taken into consideration as an alternative to BEAM as both were well tolerated.[12]

Berber *et al*. stated that the BuCyE preparation regimen could be used instead of BEAM in a study with 8 (25.8%) of 42 patients having HL. A median engraftment time for neutrophil and platelet was 12–14.5 days. The treatment-related mortality rate was 6.5% of all BuCyE patients, and 6-month OS was found 49.73%. According to this study, BEAM preparative regimen had similar results.[13]

Another trial, comparable to ours, found that the BuCyE combination was tolerated well and looked to be efficacious in those with aggressive NHL. The median engraftment day was 12 days for neutrophils and 13 days for platelets. The relapse rate was 23.4% of all patients, whereas 20.3% of them died because of disease. Two (3.1%) patients died of treatment-related problems within 30 days of transplantation. All patients had an estimated 3-year OS of 72.1%.[14]

Busulfan is an alkylating agent that has difficulty in administration because of the narrowness of the therapeutic window and pulmonary and hepatic toxicity. Although busulfan was administered intravenously at 0.8 mg/kg q 6 h from day −7 to −5 in our study, different dosages (14 mg/kg, 0.8 mg/kg, and 16 mg/kg) and administration methods (oral or parenteral) are acceptable for a preparative regimen with ASCT. Twelve-month OS was found in 77% of all patients in a study in which busulfan was used at a dose of 16 mg/kg with ASCT.[15] In another study using 16 mg/kg of oral busulfan, hepatic toxicity was found in 15% of all patients, and 3-year OS was 43%.[16] Copelan *et al*. studied 14 mg/kg of oral busulfan usage which achieved a 3-year progression-free survival rate of 46.9% in 382 patients. In addition, its utilization was associated with a low incidence of transplant-related death as well as subsequent problems such as acute myeloid leukemia and myelodysplasia.[17]

The development of Pk-directed dosage modification for Bu aimed to prevent unpredictably high doses of the drug. As a result, in the preparative regimen with ASCT, Pk-directed dosages of Bu (on days −8 through −5), etoposide (1.4 g/m^2 on day 4), and cyclophosphamide (2.5 g/m^2 on days 3 and 2) were administered. Two-year OS was 76% for HL patients and 67% for DLBCL. This study compared BuCyE and BEAM and found no significant difference between the two studies in 2-year OS in HL patients. In addition, busulfan dosage was modified by PK, which showed better adverse effect profiles and engraftment outcomes.[18] When looking at the side effects with BuCyE, they were found to be similar to other protocols except for pulmonary side effects.[19,20]

A multicenter study of intravenous BuCyE was made in Korea which used a similar preparative regimen as this study. The most common histological subtype was DLBCL (40.6%). The median engraftment time for neutrophil was 12 days and for platelet was 13 days. 3.1% of all patients died from treatment-related complications. At a median follow-up of 16.4 months, 23.4% of all patients exhibited a relapse or progression, whereas 20.3% of all patients died from the disease. The estimated 3-year OS for all patients was 70.1%, respectively.[14]

Post-ASCT consolidation constitutes future discussions on this subject. Brentuximab vedotin,[21] nivolumab,[22] and pembrolizumab[23] are drugs that have been studied for consolidation. Studies examining even consolidations with antibody–drug conjugate and checkpoint inhibitor combinations (brentuximab vedotin with nivolumab) have shown that 2-year OS in patients with r/r HL has reached 90%, respectively.[24]

Conclusion

There are a lot of studies about BEAM and NHL patients. It seems less study evaluated the preparative regimen of low-dose BuCyE against HL. The experience with the BuCyE regimen is mostly with NHL patients in the literature. The BuCyE regimen may be a good alternative to BEAM for ASCT in patients with r/rHL. We state that new and large studies are needed to strengthen our findings.

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Conflicts of interest
There are no conflicts of interest.

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