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Evaluating the Efficacy of Modified BeEAM (Bendamustine, Etoposide, Cytarabine, Melphalan) Regimen as Conditioning for Autologous Stem Cell Transplantation in Relapsed or Refractory Lymphoma: An Experience from Two Centers of a Developing Country

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ABSTRACT

Background: High-dose chemotherapy followed by Autologous SCT (stem cell transplantation) is a treatment of choice for relapsed and refractory lymphoma. Due to cost, toxicity, and shortage of Carmustine, we decided to conduct a phase 2 clinical trial to evaluate the safety and efficacy of Bendamustine instead of Carmustine in a previously used BEAM-like protocol.

Materials and Methods:102 patients (median age,37) with Hodgkin(n=54) and non-Hodgkin lymphoma(n=48) were recruited and transplanted in two centers. After stem cell harvesting, a modified BeEAM regimen was administered to all the patients. Overall survival and disease-free survival (DFS) at two years were calculated as the study's primary endpoints.

Results: Neutrophil and platelet recovery were observed after a median of 12 and 13 days, and all the patients were engrafted. Fever was observed in 25(24.5%) with only two documented infections. The only grade III toxicities were mucositis (20%) and nausea (15.6%). No transplant-related mortality (TRM) was observed after 100 days. After a median follow-up of 37(range 25-48) months, 68(66.6%) patients were in complete remission while 21 patients were in partial response, and 16 patients (15.6%) developed progressive disease, among which 13 (12.7%) had died. The OS at two years was (89 of 102, 87.3%), and the DFS rate was 68 of 102(66.7%).

Conclusion: Our study showed that modified BeEAM is a safe, effective, and feasible conditioning regimen for ASCT in lymphoma instead of the BEAM regimen.

Keywords: Autologous stem cell transplant; Lymphoma; BeEAM

INTRODUCTION

Transplantation of hematopoietic stem cells (HSCT) has been accepted as the standard treatment for many diseases, such as congenital or acquired hematopoietic system disorders and chemo, radio, or immune-sensitive malignancies. HSCT has undergone rapid expansion over the past three decades. Despite the high cost and the complexity,

the HSCT procedure has developed in our country as a developing country[1].

The shortage of drugs and procedures and their cost is a problem in our country, especially in the transplant field. So we need to evaluate and change the standard regimen in our center according to the availability and cost of drugs. Sometimes, it may result in better outcomes, more feasibility, and less toxicity [2].

High-dose chemotherapy (HDCT) followed by autologous hematopoietic cell transplantation (autoHCT) is a standard therapeutic option for most patients with chemosensitive relapsed or refractory lymphoma.

With improvement in supportive care and management of toxicity resulting from the conditioning regimen, the survival rates after ASCT are approaching 60% for B cell lymphomas [3] and 40–70% in patients with HL[4].

BEAM (Carmustine, etoposide, cytarabine, melphalan) is the most common regimen used as conditioning before autoHCT for patients with RR lymphomas[5]. To potentially increase the efficacy [6-7]and reduce pulmonary toxicity [8-9], other agents like thiotepa, lomustine, or Bendamustine have been proposed to replace Carmustine (TEAM, CEAM, and BeEAM, respectively) [2,10,11].

Visani et al. (2008) for the first time replaced Bendamustine with Carmustine in BEAM for ASCT of relapsed/resistant lymphomas with 100 days of transplant-related mortality (TRM) of 0%[6]. The efficacy and safety of BeEAM were initially evaluated by Visani et al. in a prospective study including 43 patients with HL and NHL. TRM was 0%, while the cumulative incidence of infectious complications was 60%, without non-hematological serious adverse events. The study revealed that the new protocol was safe and effective, especially for heavily pretreated patients[6]. The updated follow-up at 41 months after transplant showed a 72% probability of PFS at three years [7].

Bendamustine was first synthesized in Germany with better efficacy and less toxicity than other alkylating agents[12].

Bendamustine combines the alkylating activity of the nitrogen mustard group with the antimetabolite activity of the purine analog structure (benzimidazole ring)[12]. This characteristic makes it an attractive option to replace Carmustine. Given the uniqueness of its chemical structure, it has a different mechanism of action from traditional alkylating agents. Carmustine demonstrates only partial cross-resistance with other alkylating agents. Its mechanisms of action include activation of DNA-damage stress response and apoptosis, inhibition of mitotic checkpoints, and induction of mitotic catastrophe[13]. So this drug can be used in malignancies resistant to other alkylating agents.

Carmustine's (BCNU) shortage and cost were problems in our country; therefore, we decided to evaluate other regimens in our center. We used a new and modified regimen, CEAM, to replace BEAM in our center for many years [2].

Recently, after encouraging results from a study by Visani et al., reporting a three-year PFS of 72%[7] and demonstrating efficacy and manageable toxicity of co-treatment of Bendamustine with etoposide, cytarabine, and melphalan, we have used modified BeEAM as the conditioning regimen for ASCT to treat relapsed/refractory lymphoma at our institution.

Here, we present the results from using the BeEAM protocol for more than three years. The purpose of the present retrospective study was to provide information on the potential risks and benefits of Bendamustine-based high-dose regimens for auto-SCT in H lymphoma and NHL.

MTERIALS AND METHODS

Patients Population

All patients with relapsed/refractory lymphoma were admitted to two Bone marrow transplantation (HSCT) centers in Shiraz university of medical sciences, Namazee, and Amir Hospitals in three years included in this study. Exclusion criteria were ECOG performance status ≥2, the inadequate number of CD34+ cells for stem cell transplant after harvesting, and age<17. In this study we evaluated the efficacy and outcome of BeEAM conditioning in cases who adequate number of CD34+ cell have been harvested after mobilization (at least>2×10^6 /kg of body weight of patient). All included patients signed written informed consent. The study was conducted according to the Helsinki protocol, approved by the Ethics Committee of Shiraz University of Medical Sciences.

High dose therapy and Transplantation

Bendamustine 120mg/m^2/day intravenously as 2 hours infusion, cytarabine 600mg/m^2/day intravenously in 2 hours, Etoposide 500mg/m^2/day intravenously in 6 hours all on day -3 to -2 and melphalan 140mg/m^2/day intravenously on day -2 followed by stem cell reinfusion at day 0.All the patients received peripheral blood stem cells. Mobilization of stem cells was done with GCSF alone with a dose of 5µg/kg two times per day for four days.

After the transplant, GCSF with a 5µg/kg dose was subcutaneously administered when ANC dropped below 0.5 g/L and continued till neutrophil recovery. Transfusion of irradiated packed red blood cells and platelets was done if Hb<80g/L and Plt< 20×10^9 /L. Ciprofloxacin 500 mg and fluconazole 100 mg twice daily were used as antibiotics and antifungal prophylaxis. Also, acyclovir 400 mg three times daily was administered as antiviral prophylaxis. If a patient had developed a fever, the broad-spectrum antibiotic was started after obtaining cultures and continued till neutrophil recovery and no fever for 48 hours. Acyclovir continued for three months post-transplant. Patients were treated in single rooms with isolation and discharged after acceptable hematologic recovery. After discharging the patients from the hospitals, they were visited at the transplant clinic weekly, recording their signs, symptoms, and lab data until three months. CT scan was done every three months for response evaluation.

Definitions

Disease status was evaluated by RECIST 1.1 criteria. Unfortunately, most patients did the contrast CT scan instead of the PET-CT scan due to cost and unavailability. Overall survival (OS) was defined as the time of transplantation to death. DFS was measured as the time from transplantation till progression, relapse, or death, whichever happened first. Adverse events due to treatment were graded according to Common Terminology Criteria for Adverse Events (CTCA) 4.0.

Statistical analysis

Descriptive statistics, including percentage and frequency, and mean ± standard deviation was used to describe the data. Survival analysis was performed using the Kaplan-Meier method to produce survival curves for DFS and OS. Data were analyzed using Statistical Package for Social Science (SPSS 23.0).

RESULTS

One hundred and two relapsed/refractory lymphoma patients (HD=54, NHL=48) were recruited in this study. The number of patients with complete and partial remission at transplantation time was 67(65.7%) and 35(34.3%), respectively. Detailed characteristics are shown in Table 1. The median age of patients was 37(17-61) years old. The most common pathology in the NHL group was Diffuse Large B-cell Lymphoma (n=45, 44.1%). The median number of therapies line, including induction, was 2[2-5].The majority of patients were in complete remission at transplantation time (n=67, 65.7%).

Hematologic findings

The median 3.55×10^6 (range,1.9-11.4) CD34+cells/kg body weight was reinfused for the patients. Median days for neutrophil recovery with ANC>0.5 g/L and platelet recovery with Plt>20×10^9 were 12days (range, 8-21) and 13 days (range,8-27), respectively. The median dose of packed RBC and Platelet transfusion was 2 (range, 1-4) and 13(range, 4-35). The median days of admission were 22 days (16-35). Patients received a median of 9 days (range, 6-21) of GCSF post-transplant (Table 2).

Fever and Infection

Twenty-five patients (24.5%) developed fever, but with positive blood culture, bacteremia was documented in only two patients (2%) with Klebsiella. No patient developed viral or systemic fungal infection. Median days of fever were 4 (range, 2-10), and median days of antibiotic therapy was 7 (range, 4-15) days.

Non-hematologic toxicity

The most observed toxicity was nausea and vomiting, which occurred in all the subjects, but only 16(15.6%) developed grade 3 toxicity, and no parenteral nutrition was necessary. Another major toxicity in our study group was mucositis in 90% of patients, but toxicities in grade 3 were seen in 22(21.5%). Also, grade III liver toxicity with abnormal liver function tests and grade III diarrhea were detected in 5 patients (5%) and 3(3%), respectively. No grade 3/4 renal dysfunction and no episode of cardiac toxicity or Veno-occlusive disease were observed. One (1%) of the patients suffered from grade 2 pulmonary toxicity, relieved with supportive care. Three months after discharge, we did not observe any hospitalization due to transplant toxicity.

Outcomes

After the transplantation, patients had a CT scan every three months for one year and then every six months. In our study, 15(14.7%) patients with partial remission entered into complete remission after transplantation that lasted 24 months in our follow-up. After median follow up of 37 months (range, 25-48), 68 patients (66.7%) were in complete remission, 21patients were in partial response while 16 patients (15.6%) developed with progressive disease among which 13(12.7%) had died. It must be mentioned that seven of the patients were not in complete remission at enrollment, so there were relatively chemoresistant in this group. After a median follow-up of 37 months (range, 25-48), the OS was (89 of 102, 87.3%), and the DFS rate was 68 of 102=66.7% (Figures 1, 2).

Table 1: Patients Characteristics

Median age, y(range)	**37(17-61)**
Sex	
Male	63
Female	39
Disease Type	
Hodgkin	50
Non-Hodgkin	48
DLBL	39
ALCL	1
Primary mediastinal B-cell lymphoma	2
Brian lymphoma	3
Mantle	1
T-Cell lymphoma	2
NLPHL	4
Median time to transplant,m(range)	12(4-60)
Disease stage at diagnosis	
2	45
3	20
4	37
Remission status before transplant	
Complete remission,n(%)	68(66.7%)
Partial remission,n(%)	21(20.6%)
Median number of therapies	2
Previous therapies	
ESHAP	59
IEV	17
ICE	6
GDP	15
DHAP	4
EPOCH	5
Radiotherapy	19
Bulky disease	
Yes	21
No	81

Table 2. Hematologic recovery

CD34+ CELLS/kg/body weight, n(range)	**3.55×10^6 (1.9-11.4)**
Median days for ANC>0.5 g/L	12(8-21)
Median days for Plt>20×10^9	11(8-27)
Median days of admission	22 (16-35)
Median days of GCSF administration	9(6-21)
Median number of packed red cell infusion	2 (1-4)
Median number of platelet infusion	13(4-35)

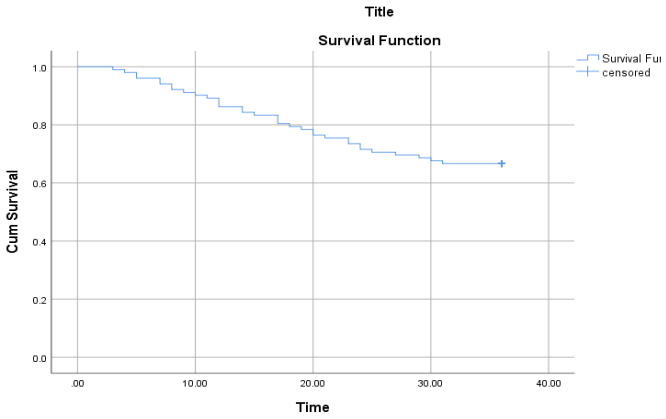

Figure 1: Disease-free survival after transplantation

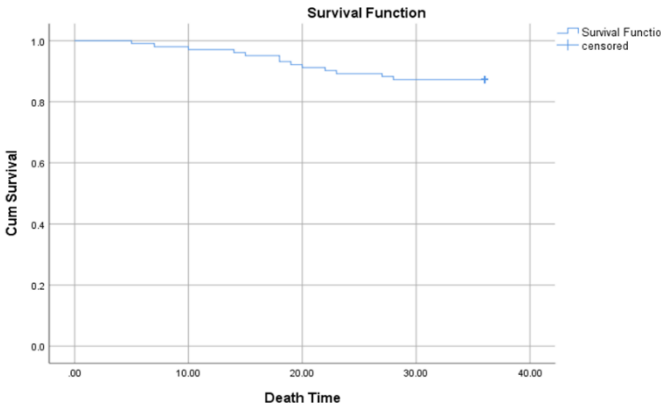

Figure 2: Overall survival after transplantation

DISCUSSION

Although HDCT followed by auto HCT is considered the treatment of choice in chemosensitive RR lymphomas, the standard conditioning chemotherapy regimen has not yet been defined. BEAM (Carmustine, etoposide, cytarabine, melphalan) is the most common regimen used as conditioning before auto HCT for patients with RR lymphomas [5]. Carmustine was associated with the risk of pulmonary toxicity manifested by interstitial pneumonia. To avoid this complication and potentially increase the regimen's efficacy, it has been suggested that Bendamustine be used instead of Carmustine. The efficacy and safety of BeEAM were initially evaluated by Visani et al. in a prospective study including 43 patients with HL and NHL. TRM was 0%, while the cumulative incidence of infectious complications was 60%, without non-hematological serious adverse events. The study revealed that the new protocol was safe and effective, especially for heavily pretreated patients[6]. The updated follow-up at 41 months after transplant showed a 72% probability of PFS at three years [7].

Moreover, the cost, shortage of production, and unavailability of Carmustine in our country led us to conduct a phase two clinical trial study to evaluate DFS and OS in relapsed/resistant lymphomas in our two Bone Marrow Transplantation centers at Shiraz University of Medical Sciences: Namazee and Amir Hospitals.

Due to the reported renal, cardiac, and hepatic toxicity of Bendamustine in high and intermediate doses in previous studies (14,15), our patients received a reduced dose of 120mg/m2 /day for two days. TRM at 100 days was 0% in our study, as reported by Visani and colleagues and Saleh et al. [16]

The most common toxicity in our study was mucositis in 79%(grade III in 21%) and nausea in 91%(grade III in 19%), comparable to other GI toxicity [14-16]. No cardiac toxicity was observed in our study group. Only two (2 %) of patients developed grade III liver toxicity and one with grade II pulmonary toxicity in our study. Chantepie et al.[14] reported a 27.9% incidence of acute renal failure[14] with a median bendamustine dose of 196mg/m2, but we only detected in 5(5%)that could be due to a lower dose (120mg/m2) of Bendamustine in our study.

We used 120 mg/m2 of Bendamustine for two days. With this dose reduction, we did not observe significant renal and other toxicities without any change in outcomes. Therefore, we believe that the appropriate dose and schedule of Bendamustine require further study.

Although fever occurred in 24.5% of cases, microbial pathogens were found in only 2%. While 14% of patients showed evidence of infection, the fever may be due to causes other than an infection. This is contrary to the study of Gilli et al. [17], in which all patients developed fever and four ICU admissions were necessary due to septic complications. A large retrospective study conducted on 474 patients treated with the BeEAM regimen reported a very high rate of infections with 78% of cases [14]. The lower rate in our study group may be due to prophylactic antibiotic use in our patients after catheter insertion. Recently Hahn L et al. reported a retrospective study about their experiences with 41 lymphoma patients with BeEAM HDCT regarding safety, efficacy, and cost-saving. They compared OS and PFS to a cohort of 86 patients previously transplanted at their center with the old BEAM standard regimen. They found no statistically significant difference between BeEAm and BEAM[18]. In this study, the prevalence of oral mucositis amongst BeEAM patients was 88%, which is concordant with other previous studies. Still, they reported grade III-IV mucositis only in two patients (4.9%), which differed from our results (22% grade III) and Visani et al.'s report (25%)[6]

In our study, after a median follow up of 37 months (range,25-48), 68 patients (66.6%) were in complete remission, 21patients were in partial response, while 16 patients (16%) developed progressive disease, among which 13 (13%) had died. Our results were compatible with previous studies in which survival analysis suggests comparable results for BeEAM and BEAM[6,7,18].

According to our result, with BeAEM regimen after a median follow-up of 37 months (range,25-48), the OS was (89 of 102) 87.3%, and the DFS rate was(68 of 102) 66.7%, which is comparable and still better than previously reported of CEAM regimen by our center in which the 2-year OS was 84%.

One important controversy in the results of BeAEM studies reported in the literature is the wide range of renal toxicity. The incidence of nephrotoxicity has been reported to be between 1.6%-48% [15-16, 19-21]. Noesslinger et al. found that almost 80% of BeEAM patients experienced transient increases in creatinine within a few days of bendamustine administration[21]. However, none of these patients required any therapeutic intervention or delays in the administration of chemotherapy[21]. Based on these results, there is a need for a large prospective multicentric randomized clinical trial for exact and further evaluation of the safety and toxicity of BeEAM protocol in ASCTof lymphoma.

Limitations of our study included low sample size, short follow-up, and performing imaging to determine the stage of patients in different centers, resulting in different interpretations. Future studies with larger sample size and uniform follow-up protocols are necessary.

CONCLUSION

Administration of Bendamustine instead of Carmustine as part of conditioning does not affect the engraftment, survival analysis, or the toxicity profile of the regimen. Therefore, BeEAM may be safely and effectively used in patients with lymphoma undergoing auto-HCT. Its efficacy requires more evaluation in more extensive randomized clinical trials in the future.

Therefore, we conclude that Bendamustine may safely replace Carmustine in preparative regimens for patients with lymphoma referred for auto HCT.

These results indicate that the efficacy and tolerability of bendamustine-based regimens might be similar to that of conventional BEAM. We can suggest modified BeEAM as a conditioning regimen based on available data instead of a BEAM regimen.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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