Safety and efficacy of bendamustine in the conditioning regimen for autologous stem cell transplantation in patients with relapsed/refractory lymphoma

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Background
Bendamustine is an attractive option for the management of both de novo and relapsed lymphomas. It is being increasingly used in the conditioning regimen for autologous stem cell transplantation (SCT) and can be an alternative to the traditionally-used carmustine. In this study, we aimed to determine the safety and efficacy of bendamustine in the conditioning regimen for autologous SCT in refractory/relapsed lymphomas.

Methods
We designed a descriptive study to evaluate bendamustine in combination with etoposide, cytarabine, and melphalan (BeEAM) in the conditioning regimen for autologous SCT.

Results
Fourteen patients (median age, 28 yr) with Hodgkin's lymphoma (HL) (N=8), non-Hodgkin's lymphomas (NHL) (N=5), or peripheral T-cell lymphoma, not otherwise specified (PTCL NOS) (N=1) were included in the study. A median number of 5.95×10^6 CD34+ cells/kg were transfused. Median times to absolute neutrophil count and platelet engraftment were 17 days and 24 days, respectively. The 100-day transplantation mortality rate was 28% (4 patients). Eight patients (57.14%) had GII-III acute kidney injury, four patients (28.5%) had GIII-IV hyperbilirubinemia, and twelve patients (85%) had GII-III diarrhea. After 3 months, 37% (5 patients) and 21.4% (3 patients) demonstrated complete response and partial response, respectively. The median follow-up was 5.5 months (15 days–19 mo). At the final follow-up, 7 patients (50%) were alive and in CR.

Conclusion
Our study showed that bendamustine is a potentially toxic agent in the conditioning regimen for autologous SCT, resulting in significant liver, kidney, and gastrointestinal toxicity. Further studies are required to assess its safety and efficacy at reduced doses.

Key Words   Bendamustine, Toxicity, Autologous stem cell transplant, Lymphoma

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INTRODUCTION

Hodgkin's lymphoma (HL) and non-Hodgkin's lymphomas (NHL) are highly chemotherapy-sensitive tumors. However, there is a significant subset of patients who relapse or who never achieve complete remission. Second line salvage chemotherapy has been shown to be very effective in patients with chemosensitive diseases with CR rates greater than 50%, as observed with aggressive second line chemo immunotherapy in relapsed diffuse large B cell lymphoma (DLBCL) [1, 2].

However, the prognosis is usually poor with conventional salvage regimens alone [3, 4]. High dose therapy (HDT) followed by stem cell rescue is the treatment of choice for patients with relapsed/refractory lymphoma. Philip *et al.* [5] demonstrated a statistically significant difference in 5-year event-free survival (46% vs. 12%; *P*=0.001) and OS

(53% vs. 32%; P=0.038) for patients undergoing autologous stem cell transplantation (ASCT) and salvage chemotherapy, respectively. 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 [6] and 40–70% in patients with HL [7, 8].

Carmustine, etoposide, and cytarabine with melphalan (BEAM) is the most common conditioning regimen used for ASCT for relapsed lymphoma. Other regimens that have been studied include cyclophosphamide (BEAC), cyclophosphamide, carmustine, and etoposide (CBV), and cyclophosphamide-TBI (total body irradiation), but BEAM remains the preferred conditioning regimen [9, 10]. Recently, availability of carmustine has been problematic in certain parts of the world. Therefore, there is increasing interest in exploring other active agents that could potentially replace carmustine in the conditioning regimen for ASCT. Bendamustine is an attractive option to replace carmustine because it combines the alkylating activity of the nitrogen mustard group with the antimetabolite activity of the purine analog structure (benzimidazole ring). Given the uniqueness of its chemical structure, it has a different mechanism of action from traditional alkylating agents. Carmustine demonstrates only partial cross-resistance (*in vitro*) with other alkylating agents. It leads to cell death via single and double strand DNA cross-linking, and has also been shown to activate apoptotic pathways [11]. Therefore, bendamustine has clinical potential for treating diseases that are refractory to alkylators. It has shown superior efficacy compared to standard therapies for relapsed chronic lymphocytic leukemia and indolent NHL [12], and is considered a standard first line treatment for indolent B cell lymphoma [13]. These data make it an attractive option as part of the conditioning regimen in ASCT.

Carmustine is not available in Pakistan. After encouraging results from a study by Visani *et al.* [14] demonstrating efficacy and manageable toxicity of cotreatment of bendamustine with etoposide, cytarabine, and melphalan, we have been exclusively using bendamustine, cytarabine, etoposide, and carmustine (BeEAM) as the conditioning regimen for ASCT to treat relapsed/refractory lymphoma at our institution. Here, we present the safety and efficacy data from use of the BeEAM protocol from the last 2 years.

MATERIALS AND METHODS

Patient population

Fourteen patients with resistant/relapsed lymphomas, including both NHL and HL, were included in this study. Patient files were retrospectively reviewed to collect data regarding their diseases, treatments, toxicities, and outcomes. This protocol was approved by the Ethical Review Committee of Aga Khan Hospital, Karachi.

Mobilization and conditioning regimen

Patients were mobilized with granulocyte colony stimulating factor (GCSF) (5 mg/kg, twice per day subcutaneously for 4 days) or cyclophosphamide. Patients that received cyclophosphamide (1.5 g/m^2) then received GCSF (5 mg/kg, twice daily subcutaneously for 6 days). Patients that underwent mobilization with GCSF alone underwent scheduled stem cell pheresis on day 4. For patients who received cyclophosphamide and GCSF mobilization, stem cells were harvested on days 5 to 7 (depending on count recovery) using either a Cobe Spectra AutoPBSC or a COMTEC (Fresenius Kabi, Bad Homberg, Germany) system in the default software configuration recommended by the manufacturer. After stem cell collection, patients received the conditioning regimen, which consisted of bendamustine coupled with fixed doses of etoposide, cytarabine, and melphalan (BeAM) administered in an inpatient setting. BeAM regimen was given per standard protocols and institutional guidelines. Hyperhydration was started on day -6, followed by bendamustine 150 mg/m^2 (days -5 and -4), etoposide 150 mg/m^2 (days -5 to -2), cytarabine 150 mg/m^2 (days -5 to -2), and melphalan 75 mg/m^2 (day -1). Stem cell infusion was performed on day 0. All patients received granulocyte colony stimulating factor (GCSF) from day +1.

Supportive care and monitoring

A central line was inserted in all patients. They were admitted to a single room, and reverse barrier nursing was practiced. All patients were given antimicrobials (levofloxacin 500 mg od or ciprofloxacin 500 mg bid), an antifungal (voriconazole 200 mg qd), and an antiviral (valacyclovir 500 mg bid) as prophylaxis starting at day -5. Blood tests were performed per standard protocols, and blood products were transfused to keep hemoglobin levels >8 g/dL and platelet count >15×10^9. In cases in which fever developed, patients were given intravenous broad-spectrum antibiotics. Piperacillin tazobactam or imipenem/meropenem were given for gram negative bacilli coverage. Vancomycin was the drug of choice for management of gram positive cocci. In addition, amphotericin B was used when fungal infections were suspected. Patient symptoms were assessed daily, and physical examinations were administered during their hospital stay and as per recommendations after follow-up.

Response criteria

Engraftment was defined as achievement of an absolute neutrophil count of 0.5×10^9 per liter for 3 consecutive days. Platelet engraftment was defined as a count of 20×10^9 per liter with transfusion independence. Patients were evaluated for response at 4 weeks after transplant, and then at day 100, at the outpatient clinic. At subsequent follow-up visits, imaging was performed per the discretion of the treating physicians. All toxicities were defined using the National Cancer Institute's Common Terminology Criteria for Adverse Events Version 3.0 (2003). All patients were evaluated using either computed tomography (CT) or positron emission tomography (PET) before and after ASCT.

Statistical analysis

The primary end point was to assess the safety and efficacy of bendamustine in the conditioning regimen for autologous stem cell transplantation in patients with relapsed/refractory lymphoma. The secondary objectives included assessment of time to progression and overall survival. Statistical analysis was performed in accordance with approved protocols. The Kaplan-Meier method was used to estimate overall survival. Data were analyzed using Strata 12.1 software.

RESULTS

Patient characteristics

Patient characteristics are summarized in Table 1. Fourteen patients were included in this study. The median age of the included patients was 28 years (range, 16–58 yr). Eleven (78.5%) patients were males and three (21.43%) patients were females. Eight patients (57.14) had Hodgkin's Lymphoma, five patients (35.71%) had Diffuse Large B cell Lymphoma, and one patient (7.14%) had peripheral T-cell lymphoma, not otherwise specified (PTCL NOS). DHAP/

RDHAP was the most commonly used regimen as a second line treatment (11 patients, 78.5%). Two patients (14.29%) received RICE/ICE. Eight patients (57.14%) were in CR at the time of transplant and six patients (42.86%) were in partial response.

Engraftment

The median number of CD34+ cells infused was 5.95×10^6 cells per kilogram body weight (range, 3–17.2×10^6 cells per kg body weight). No engraftment failures were noted. The median number of days on GCSF was 24 (range, 13–40 days). The median time to neutrophil engraftment was 17 days (range, 14–29 days), and 24 days for platelet engraftment (range, 13–55 days) in our cohort. The average length of hospital stay was 20 days (range, 13–45 days).

Non-hematological toxicity

Electrolyte imbalances were a frequent complication in our patients. Serum potassium abnormalities were the most common with 7 patients (50%) experiencing grade III (GIII) hyperkalemia and 7 patients (50%) experiencing GI-II hypokalemia. Nine patients (64.28%) experienced gastrointestinal (GI) hypomagnesemia. Liver dysfunction was also a common side effect in our cohort. Eight patients (57.14%)

Table 1. Patient characteristics.

Characteristics	N	%
Age, median	14	28 yr
Sex		
Male	11	78.57
Female	3	21.43
BMI, median	14	25.5
IPI		
0	3	21.4
1	6	42.8
2	2	14.2
3	3	21.4
Diagnosis		
Hodgkin's lymphoma	8	57.14
Diffuse large B cell lymphoma	5	35.71
PTCL NOS	1	7.14
Response to initial treatment		
CR	7	50.00
Refractory	2	14.29
Progressive	5	35.71
Response to relapse therapy		
CR	8	57.14
PD	1	7.14
PR	5	35.71
No. of treatment prior to transplan		
2	11	78.57
3	2	14.29
4	1	7.14
Disease status at time of transplant		
CR	8	57.14
PR	6	42.86

Abbreviations: CR, complete response; IPI, indicates international prognostic index; PD, progressive disease; PR, partial response; PTCL NOS, peripheral T-cell lymphoma, not otherwise specified.

Table 2. Nonhematological toxicity.

Adverse effect	Grade I-II	Grade III-V
Electrolyte imbalances		
Hypokalemia	7 (50%)	7 (50%)
Hypomagnesemia	10 (71.4%)	1 (7.1%)
Gastrointestinal toxicity		
Mucositis	5 (35.7%)	3 (21.4%)
Diarrhea	8 (57.1%)	5 (35.7%)
Nausea/vomiting	7 (50%)	1 (7.1%)
Abdominal pain	3 (21.4%)	
Upper GI bleed	2 (14.2%)	
Lower GI bleed	1 (7.1%)	
Hepatotoxicity		
Increase transaminases		1 (7.1%)
Increase ALP	4 (28.5%)	
Hyperbilirubinemia	4 (28.5%)	4 (28.5%)
Infectious complication		
Febrile neutropenia		13 (92.85%)
Pneumonia		4 (28.5%)
Septic shock		4 (28.5%)
CMV infection		1 (7.1%)
Renal toxicity		
Acute kidney injury	5 (35.7%)	4 (28.5%)
Respiratory toxicity		
Pleural effusion		3 (21.4%)
Respiratory failure		7 (50%)
Cardiotoxicity		
Elevated troponins	2 (14.2%)	2 (14.2%)
Arrhythmia		1 (7.1%)
CNS toxicity		
Seizures	1 (7.1%)	2 (14.2%)

had mild hyperbilirubinemia and four (28.5%) patients experienced GIII-IV toxicity. Nine patients (64.29) had acute kidney injury, among which eight patients (57.14%) experienced GII-III toxicity. Three patients (21.4%) had GIII-IV pleural effusion. Seven patients (50%) developed respiratory compromise requiring O_2 and NIV support. Eight (57.14%) patients developed mucositis, of which five patients developed GI-II mucositis and three developed GIII mucositis. Gastrointestinal toxicity was seen in all of our patients. Twelve patients (85%) developed GII-III diarrhea during their hospital stays. Cardiotoxicity was also observed in our cohort. Four patients exhibited increased troponin, of which two patients had GIII toxicity, and one patient had GIV arrhythmia.

Febrile neutropenia with GIII-IV severity was observed in 13 (92.86%) patients. Among these patients, nine had fever of unknown origin, one had a lower respiratory tract infection (LRTI), and one had both LRTI and Staphylococcus species associated CLABSI infection. One patient had septicemia secondary to *Staph epidermidis* and *E coli*. One patient had acinetobacter CMV pneumonitis as evidenced by tracheal cultures. Transplant-related mortality at day 100 was 28% (Table 2).

Outcome analysis

At the time of transplant, 8 patients (57.14%) were in complete metabolic response (CMR) whereas 6 patients (42.86%) were in PR. At day +100, 5 patients (37%) were in complete metabolic response on PET CT imaging, 3 (21%) patients showed partial response, and 2 patients (14%) had refractory disease. Transplant-related mortality at day 100 was 28%. Among 8 patients who underwent ASCT in CMR, only 2 patients remained in CR and were alive at the final follow-up. Among 6 patients who had partial response to ASCT, 5 patients were in CMR at evaluation and were alive at the last follow-up.

Patients with a low to intermediate IPI score exhibited better response and survival compared to patients who had a high IPI score. Nine patients who had low or low to intermediate IPI, 5 (55%) and one out of three patients (33.33%) with a high – intermediate IPI score patients in CMR at the last follow up.

The median time to follow-up was 5.5 months (15 days to 19 mo). At the final follow-up, 5 patients had died. Infections and subsequent systemic complications, particularly septic shock and hospital acquired pneumonia, were the most common cause of death in our cohort. Other causes included meningoencephalitis and CMV pneumonitis. At the final follow-up (median time), 7 patients (50%) remained in complete response, 2 patients (14.3%) had relapsed, and 5 patients (35.71%) had died. The median disease-free survival was 5.96 months (range, 0.46–27.96 mo) and the median overall survival was 5.42 months (range, 0.46–27.96 mo) (Figs. 1, 2).

DISCUSSION

High-dose therapy followed by ASCT is the standard of care and the treatment of choice for eligible patients with chemosensitive, aggressive, relapsed NHL and HL. This treatment has been validated by the PARMA and the CORAL studies, which demonstrated a significantly higher survival rate of greater than 50% after high-dose chemotherapy and autologous bone marrow transplantation than after conventional chemotherapy [15]. Despite the improved survival rates provided by HDT/ASCT, applicability of this treatment to all relapsing patients is limited. Several factors impacted survival. Disease status is an important predictive factor for survival. Transplant-related morbidity and mortality is another important determinant of outcome.

The BEAM protocol has been the conditioning regimen of choice for ASCT since the initial report by Mills *et al.* [8] published in 1995. They reported that 5-year overall survival and progression-free survival rates were 41% and 35%, respectively, with an early procedure-related mortality
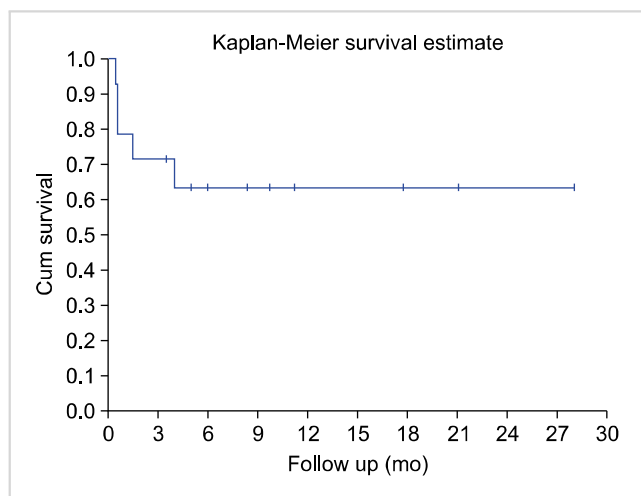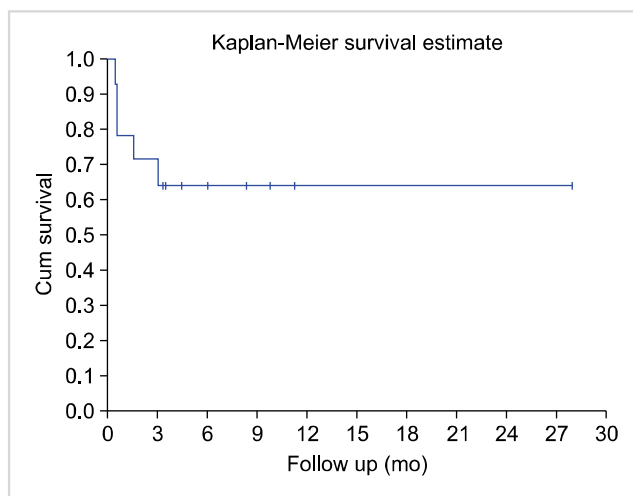

Fig. 1. Overall survival.

Fig. 2. Disease free survival.

rate of 7%. Over the years, improvement in patient selection, mobilization techniques, and supportive care has resulted in survival of greater than 70%, and TRM rates less than 2% [16, 17]. A retrospective review published by Reid *et al.* [18] showed a trend toward better 3-year OS and PFS in response to an outpatient BEAM regimen compared to an inpatient BEAM regimen. This was also accompanied by a better toxicity profile. Furthermore mBEAM showed good tolerability, with the most frequently observed non-hematologic toxicity being oral mucositis, mainly of grade I/II (47%). This tolerability was better than the BEAM regimen [11] or variants such as FEAM5 and BeEAM [19].

Late toxicities, however, remain a serious concern. Studies have revealed that non-infectious interstitial pneumonitis resulting from BCNU-containing regimens was a serious complication, reported in 16–60% of the patients, with an associated mortality rate of 9% [8, 20]. BCNU-containing conditioning regimens have also been associated with an increased risk of non-relapse mortality when compared with other regimens [19-23]. Many regimens have been tested, and the BEAM regimen remains the standard of care despite its known serious side effects.

Unavailability of carmustine in many parts of the world has led to efforts to develop a conditioning regimen without carmustine. Visani *et al.* [14] reported results of a Phase I/II study using increasing doses of bendamustine (160 mg/m^2, 180 mg/m^2 and 200 mg/m^2 given on day -7 and day -6) with fixed doses of etoposide, cytarabine, and melphalan (BeEAM regimen), administered as a preparative regimen for ASCT. Forty-three patients with resistant/relapsed HL (N=15) and NHL (N=28) were enrolled, with 9 in the phase I and 34 in the phase II studies. No patients experienced dose-limiting toxicity. TRM at day 100 was 0%. The follow-up period at the time of publication was 18 months, with 81% of patients alive and disease-free at that time. Mucositis and GI toxicity were the most commonly observed side effects. No grade III/IV nephrotoxicity or cardiotoxicity was reported. These encouraging results led to further studies evaluating bendamustine as a component of the conditioning regimen.

In a large French multicenter study (Lysa group), bendamustine was administered at a median dose of 191 mg/m^2/day (range, 50–250 mg/m^2/day) on days 6 and 7 with standard doses of etoposide, melphalan, and cytarabine. The results of this study highlighted early toxicities with bendamustine which may have been underrepresented in the Visani study due to small sample size. One hundred seven (28%) patients developed grade I-IV nephrotoxicity. Patients who developed ARF were also more likely to experience colitis, pneumonitis, cardiac arrhythmias, intensive care admission, and death. Multivariate analysis showed that creatinine level at day 1, bendamustine dose >160 mg/m^2, and age were independent prognostic factors for ARF. Ten percent of patients needed intensive care management, and the toxic death rate was estimated at 5% [24]. Garciaz *et al.* [25] reported increased nephrotoxicity in response to BeAM in their patients. Nine (31%) patients developed early renal toxicity before the day of reinfusion, of which four (14%) patients experienced grade 3–4 renal impairment. At day 30, the cumulative incidence of nephrotoxicity was 48% (17% of grade 3–4), whereas in the BEAM cohort, renal impairment was only observed in 7% of patients (5% of grade 3–4, $P<0.001$). As also noted by the Lysa group, patients who developed nephrotoxicity were more likely to need admission to the intensive care unit [24% of patients in the Lysa group vs. 10% of patients in the BEAM group ($P=0.07$)]. Cardiotoxicity was also more common in the BeAM group, with grade 2–3 cardiac toxicity observed in 10% of patients (vs. 2% in the BEAM cohort, $P=0.02$).

Our study showed a similar toxicity profile. Twenty-eight percent of our patients developed grade III-IV nephrotoxicity. In addition, we saw a higher incidence of grade II-IV colitis and hepatotoxicity than reported in previous studies. Septic shock and respiratory failure were observed in 28% and 50% of patients, respectively. Four patients (28%) in our cohort died in the early transplant period as a result of septic shock and its complications. The cause of the higher incidence of toxic death compared to that in other similar studies is unclear and needs further examination. One hypothesis is that higher doses of bendamustine were responsible for increased toxicity. The Lysa group reported increased toxicity at doses greater than 160 mg/m^2. In our protocol, we used 150 mg/m^2 of bendamustine at days 4 and 5. Despite this dose reduction, we observed significant toxicities. Therefore, it is our opinion the appropriate dose and schedule of bendamustine requires further study.

In conclusion, in our retrospective analysis, we reported a high incidence of renal and cardiac toxicity and an unusually high transplant-related mortality of 28% with bendamustine in the conditioning regimen for autologous stem cell transplant. Therefore, bendamustine should be used with caution. Prospective comparative studies are needed to confirm the appropriate dose and schedule of bendamustine, and to further evaluate the toxicities noted in retrospective studies before it is routinely adopted in clinical practice.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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