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Allogeneic Transplantation after Myeloablative Rituximab/BEAM +/− Bortezomib for Patients with Relapsed/Refractory Lymphoid Malignancies: 5-Year Follow-up Results

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Abstract

Although bortezomib and rituximab have synergistic activity in patients with lymphoma, and can both attenuate graft-versus-host disease (GVHD), the drugs have not been used together in patients undergoing allogeneic stem-cell transplantation (alloSCT). In this phase 1/2 trial, we assessed the safety and activity of bortezomib added to the rituximab (R) plus BEAM (carmustine, etoposide, cytarabine, melphalan) regimen in patients with relapsed lymphoma undergoing alloSCT. Primary GVHD prophylaxis consisted of tacrolimus and methotrexate. Bortezomib (1 – 1.3 mg/m^2 per dose) was administered intravenously on days −13, −6, −1, and +2. We performed inverse probability weighting analysis to compare GVHD and survival results to a historical control group that received R-BEAM without bortezomib. Thirty-nine patients were assessable for toxic effects and response. The median age was 54 years. The most common diagnosis was diffuse large B-cell lymphoma (41%). Twenty-two patients (56%) and 17 patients (44%) received their transplants

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from matched related and unrelated matched donors, respectively. The maximum tolerated bortezomib dose was 1 mg/m^2. The weighted cumulative incidences of grade II-IV and grade III or IV acute GVHD were 50% and 34%, respectively; these incidences and survival rates were not significantly different from those of the control group. Median survival has not been reached in patients age ≤50 years and who had a long follow-up time of 60.7 months. The R-BEAM regimen has a survival benefit in lymphoma patients age ≤50 years undergoing alloSCT. The addition of bortezomib has no impact on survival or incidence of GVHD.

INTRODUCTION

Allogeneic stem cell transplantation (alloSCT) is a potentially curative treatment for a wide range of hematologic malignancies [1, 2]. In patients with relapsed or refractory non-Hodgkin lymphoma (NHL), alloSCT may have several benefits over autologous transplantation owing to the graft-versus-lymphoma effects and infusion of lymphoma-free grafts [2]. Despite the use of non-myeloablative (NMA) conditioning regimens to reduce toxicity following alloSCT over the past 2 decades [2, 3], acute graft-versus-host disease (GVHD) remains a clinically significant barrier to the more widespread application of alloSCT [4, 5]. In addition, NMA conditioning regimens have been associated with inferior survival times in patients with transformed aggressive histologies or heavily pre-treated refractory disease [6–10].

One major concern regarding the use of more-intense myeloablative conditioning regimens, is the higher risk of GVHD [11] due to cytokine release and organ toxicity. Myeloablative BEAM (carmustine, etoposide, cytarabine, and melphalan) is commonly used as a conditioning regimen in lymphoma patients receiving autologous SCT [12]. We and others previously showed that as a conditioning regimen for patients with refractory lymphoma receiving alloSCT, BEAM may help enable early disease control [13, 14]. However, the regimen was associated with significantly higher incidences of grade II-IV and grade III or IV than those observed with the NMA conditioning regimen of fludarabine, cyclophosphamide (or more recently, bendamustine), and rituximab, despite the use of the same GVHD prophylaxis of tacrolimus and methotrexate [3, 15].

Several strategies to reduce the incidence of GVHD among alloSCT recipients have been investigated. Given evidence that B-cell dysregulation contributes to the pathogenesis of GVHD [16], such strategies have included adding rituximab before and after alloSCT. Rituximab has also shown promise in both the treatment [17] and prevention of GVHD [18–20]. Bortezomib might also be used to decrease the risk of GVHD. Studies in animal models have suggested that the addition of bortezomib before and immediately after transplantation significantly improves survival and delays the onset of acute GVHD, possibly by inhibiting alloreactive T cells [21]. Substantial data suggest that bortezomib and rituximab have synergistic activity in NHL patients, cell lines, and mouse models [22]. In addition, clinical trials have demonstrated tolerability and good responses in NHL patients treated with bortezomib and rituximab alone [23] or in combination to chemotherapy [24, 25]. However, bortezomib and rituximab have not been used together in patients undergoing alloSCT.

We performed a clinical trial to determine the maximum tolerated dose (MTD) of bortezomib when combined with R-BEAM and to characterize toxic effects, GVHD, and efficacy in patients with lymphoid malignancies receiving alloSCT. We also compared patients treated with this combination to a historical control group of patients who received R-BEAM without bortezomib.

PATIENTS and METHODS

Eligibility Criteria

This prospective, single-arm, phase 1/2, open-label, investigator-initiated clinical trial (ClinicalTrials.gov #NCT00439556) enrolled patients receiving treatment for relapsed or refractory NHL at MD Anderson Cancer Center from May 2007 through May 2011 who were not eligible for NMA conditioning regimens. Other inclusion criteria were age ≤65 years; an Eastern Cooperative Oncology Group performance status score of 0–2; adequate liver function, defined as a serum bilirubin level and liver enzyme concentrations ≤3 times the upper limit of normal; adequate renal function, defined as a serum creatinine level <1.8 mg/dL; adequate cardiac function, defined as an ejection fraction ≥40%; adequate pulmonary function, defined as diffusing capacity of the lung for carbon monoxide ≥40% of predictive value. Patients and donors were typed by high-resolution techniques described previously [26]. All recipients were matched with their donors at 10 of 10 human leukocyte antigen (HLA) alleles.

Major exclusion criteria included initiation of anti-cancer therapy <3 weeks before study enrollment; active disease involvement in the central nervous system (CNS); pregnancy; breastfeeding; known infection with human immunodeficiency virus, human T-lymphotropic virus, or hepatitis B or C virus; concurrent presence of other malignancies, with the exception of cutaneous squamous cell or basal cell carcinoma; uncontrolled infection; and stroke or myocardial infarction within 6 months of study entry. Other exclusion criteria included active infections requiring therapy; grade 2 or higher active peripheral neuropathy; and any prior grade 4 or higher bortezomib toxicity.

The protocol was approved by MD Anderson's Institutional Review Board, and informed consent was obtained prior to patient enrollment.

Study Design

Three bortezomib dose levels were to be evaluated: 1.0 mg/m^2, 1.3 mg/m^2, and 1.6 mg/m^2. A standard 3+3 design was employed, with the starting dose of 1.3 mg/m^2. Dose-limiting toxic effects were defined as grade 3 or 4 neurological toxicity, graft failure, or death due to GVHD at any time within the first 90 days after transplant. We used the Common Terminology Criteria for Adverse Events v3.0, which was available at the conception of the trial. Once the MTD was determined, the phase 2 portion of the trial ensued, and the 6 patients enrolled at the MTD in the phase 1 portion were included in phase 2. Using the method by Thall et al [27], we would terminate the trial if it was likely that the toxicity rate would be >20% by day 90. A separate monitoring rule was instituted for patients who received a transplant from a matched unrelated donor (MUD); if it was likely that the death

rate at day 100 would be >20% in this subgroup, enrollment of these patients would be stopped. The maximum size of the phase 2 portion of the trial was 40 patients.

Treatments

All patients received the BEAM conditioning regimen consisting of intravenous carmustine (300 mg/m^2 on day −6), etoposide (100 mg/m^2 every 12 hours on days −5 through −2 for a total of 8 doses), cytarabine (100 mg/m^2 every 12 hours on days −5 through −2 for a total of 8 doses), and melphalan (1 dose of 100 mg/m^2 on day −1).

All patients received primary GVHD prophylaxis consisting of tacrolimus (0.015 – 0.03 mg/kg starting on day −2) and methotrexate (5 mg/m^2 on days 1, 3, and 6). Patients who received a transplant from an MUD received an additional dose of methotrexate (5 mg/m^2 on day 11) and rabbit antithymocyte globulin (ATG) (1 mg/kg intravenously on days −2 and −1). Tacrolimus tapering was initiated in patients with no active GVHD 6 months after alloSCT.

All patients received rituximab (375 mg/m^2 intravenously on day −13 and 1000 mg/m^2 on days −6, +1, and +8) as described previously [3, 4, 15]. Bortezomib was administered on days −13, −6, −1 and +2. Patients received supportive care with antibiotics, antifungals, antivirals, growth factors and immunizations as per institutional guidelines.

Clinical Evaluation

Acute GVHD and chronic GVHD were graded using standard criteria [28, 29]. Late acute GVHD was not considered to be chronic unless overlap features were present. This clinical trial did not use the National Institutes of Health (NIH) Staging System for the diagnosis and severity assessment of chronic GVHD because both this trial and the one involving the control group were conceived before the NIH diagnostic system was initially published [30], and long before this staging system was validated.

Pre-SCT disease status and post-SCT responses were assessed using standard criteria for lymphoma [31] and chronic lymphocytic leukemia (CLL) [32]. Patients were evaluated 1, 3, 6, and 12 months after alloSCT; then every 6 months for up to 5 years; and yearly thereafter. Donor chimerism and engraftment were assessed using polymerase chain reaction–based methods as described previously [4].

Statistical Analysis

Overall survival (OS) was the time from the date of transplantation to the date of death or last follow-up; patients alive at last follow-up were censored. Progression-free survival (PFS) was the time from the date of transplantation to the date of disease progression, death, or last follow-up; patients alive with no disease progression at last follow-up were censored. The Kaplan–Meier method [33] was used to estimate OS and PFS. Differences in OS and PFS between the groups were assessed using the log-rank test. Associations between OS or PFS and variables of interest were determined using univariable and multivariable Cox proportional hazards regression.

Clinical and transplant measures of interest included histology (indolent versus aggressive); age (>50 versus ≤50 years); hematopoietic cell transplantation (HCT)-specific comorbidity index; donor type; disease status at study entry; number of prior therapies; elevated serum LDH at study entry; International Prognostic Index for lymphoma patients; fluorine 18–labeled fluorodeoxyglucose positron emission tomography (PET) status at study entry; number of CD34 cells/kg infused; recipient-donor sex-, cytomegalovirus (CMV) serology-, and ABO patient-donor mismatch; the use of ATG; and the presence of severe (II-IV and III or IV) acute or extensive chronic GVHD.

To assess the impact of bortezomib on GVHD risk and OS, we compared the outcomes of the patients in the present study, who received R-BEAM with bortezomib, with those of a historical control group of 21 patients enrolled in a previous prospective trial of alloSCT for lymphoid malignancies between July 2000 and August 2005 (protocol ID99–411), who received R-BEAM without bortezomib. Patients in both the study and control groups received rituximab at the same dose and schedule and GVHD prophylaxis with tacrolimus and methotrexate. Differences in clinical and transplant characteristics between the groups were assessed using the Fisher's exact test or its generalization for categorical variables and the Wilcoxon rank-sum test for continuous variables.

Because the treatment groups were not randomized, we performed inverse probability weighting [34] to correct for potential bias in patients' selection for the comparison of the primary endpoint (i.e., GVHD). The logistic regression model that produced the propensity scores used to compute the inverse probability weights included patient age (≤50 years versus >50 years) and donor type (sibling versus MUD).

The cumulative incidences of non-relapse mortality (NRM) and GVHD were determined using the competing risks method. The competing risk included for NRM was relapse, and patients who were alive at last follow-up were censored. The competing risks included for GVHD were relapse and death, and patients who did not have GVHD, did not have disease relapse, and were alive at last follow-up were censored. Differences in cumulative incidences, adjusted by inverse probability weighting for GVHD, between treatment groups were assessed using sub-distribution hazards regression modeling [35].

RESULTS

Patient Characteristics

The study enrolled 40 consecutive patients who received treatment for relapsed or refractory lymphoid malignancies at MD Anderson from May 2007 through May 2011. One patient withdrew consent after enrollment, leaving 39 patients for analysis.

The demographic and baseline disease characteristics of the 39 patients who received R-BEAM with bortezomib are listed in Table 1, alongside the characteristics of 21 historical control patients who received R-BEAM without bortezomib. Among the patients who received R-BEAM with bortezomib, the most frequent histologies were diffuse large B-cell lymphoma, in 16 patients (41%), and CLL/Richter transformation, in 12 patients (31%). All patients had high-risk disease and had been heavily pre-treated; the median number of prior

treatments was 3 (range, 1–7 treatments). At the time of alloSCT, 8 patients (21%) had an HCT-specific comorbidity index ≥3, 16 (41%) had refractory disease, and 14 (36%) had active bone marrow involvement. Of 33 patients who underwent PET, 25 (76%) were positive for disease, and 6 (15%) had bulky disease.

Of the 12 CLL patients, 3 (25%) had documented Richter transformation, including 1 patient with transformation to Hodgkin disease, and 2 (17%) had suspected transformation based on refractoriness, elevated serum lactate dehydrogenase (LDH) levels, and PET-positivity at the time of transplant. One CLL patient (8%) had leptomeningeal disease, 1 (8%) had associated myelofibrosis, and 2 (17%) had 17p deletion with bulky disease refractory to chemo-immunotherapy.

Of the 27 lymphoma patients, 3 (11%) had failed to mobilize autologous stem cells prior to enrolling in the study, and 4 (15%) had extranodal involvement at their last relapse: 1 patient with CNS involvement, 1 with liver involvement, 1 with lung involvement, and 1 with both CNS and lung involvement.

Bortezomib Dose and Schedule

Three patients entered the phase 1 study and received bortezomib at a dose of 1.3 mg/m^2 administered intravenously on days −13, −6, −1, and +2, according the treatment plan. Because *C. difficile* infections causing colitis and sepsis occurred in all 3 patients (resulting in 2 patients' deaths), the bortezomib dose was decreased to 1 mg/m^2 in the phase 2 portion of the study, with oral metronidazole given prophylactically from day −6 until absolute neutrophil count (ANC) recovery to $\geq 0.5 \times 10^9$/L. No patients in the phase 2 portion of the study had *C. difficile* infections.

Transplantation and Engraftment

Twenty-two patients (56%) received transplants from HLA-compatible siblings, and 17 (44%) received them from MUDs. The source of the T-cell replete donor graft was from peripheral blood in 38 patients (97%); one patient (3%) received a marrow donor graft.

The median number of CD34 cells infused was 5.4×10^6/kg (range, 3 to 16). The median time to ANC recovery to $\geq 0.5 \times 10^9$/L after alloSCT was 12 days (range, 10 to 29). The median time to platelet count recovery to $>20 \times 10^9$/L after alloSCT was 13 days (range, 10 to 28).

All patients experienced donor cell engraftment. Thirty days after alloSCT, the median donor myeloid and T-cell values were both 100%. Donor cell recovery in patients who received transplants from siblings and those who received them from MUDs were similar.

Clinical Response

Twenty-four patients (62%) had a complete remission, 6 (15%) had a partial remission, and 4 (10%) had progressive disease. Five patients (13%)—4 who died from infections (including the 2 patients with *C. difficile* infections) and 1 who had a subdural hematoma—were not evaluable for response.

Survival

The median follow-up duration was 28.4 months (range, 0.3 to 98.9) for all patients and 64.8 months (range, 38.6 to 98.9) for patients who were alive at last follow-up. The estimated 5-year OS and PFS rates were 35% (95% confidence interval [CI], 20% to 50%) and 28% (95% CI, 15% to 43%), respectively (Figure 1).

Patients age >50 years who had a MUD transplant, refractory disease, a higher-than-normal serum LDH level (normal range, 313–618 U/L), or grade III or IV acute GVHD had significantly worse OS compared with their respective counterparts (Table 2). Patients age >50 years who had a MUD transplant and grade III or IV acute GVHD remained predictors of OS in the multivariable analysis (Table 2). The median OS of patients age ≤50 years who had sibling or MUD transplants were not reached (NR), whereas the median OS of patients age >50 years who had sibling or MUD transplants were 23.1 months and 2.9; $P = .002$.

Patients with grade III or IV acute GVHD as well as those with refractory disease were significantly associated with worse PFS when adjusting for donor type and age combination as well as LDH level (Table 3).

Toxicity

The non-hematologic adverse events in patients who received R-BEAM with bortezomib are listed in Table 4. Grade 5 toxicity occurred in the 2 patients who died from *C. difficile* infections. Grade 4 toxicity occurred in 2 patients (1 had aspergillosis, and 1 had elevated serum alanine transaminase and aspartate transaminase levels). Twenty-four patients had grade 3 toxicity, which was most commonly caused by infections, which were bacterial in 3 patients, viral in 3 patients, bacterial and viral in 1 patient, and bacterial and fungal in 1 patient. Grade 3 genitourinary toxicity was related to elevated serum creatinine levels in 2 patients and cystitis in 2 patients. Grade 3 neurotoxicity was related to confusion, including in the setting of a septic embolus in 1 patient.

Twenty-five patients have died at the writing of this manuscript. Disease recurrence was the main cause of death (n=9; 36%). Other causes included infections (n=6, including the 2 patients with *C. difficile* infections), acute GVHD (n=5), and chronic GVHD (n=4). One patient lost to follow-up died of unknown causes.

Patients with aggressive histologies, age >50 years, and grade II-IV acute GVHD had higher NRM compared with their respective counterparts. However, only grade II-IV acute GVHD remained a significant predictor of NRM when adjusting for histology and age (HR, 3.45; 95% CI, 1.18–10.12; $P = .024$).

GVHD Incidence

The cumulative incidence of grade II-IV acute GVHD among all patients was 55% (95% CI, 38% to 70%) and did not differ significantly different between patients with sibling or MUD transplants ($P = .36$) or between patients age ≤50 or >50 years ($P = .48$). There were no measures associated with the cumulative incidence of grade II-IV acute GVHD. The cumulative incidence of grade III or IV acute GVHD for all patients was 34% (95% CI, 20% to 49%). There was no significant association between grade III or IV acute GVHD and

donor type or age. However, MUD transplant recipients age >50 years had a higher risk of grade III or IV acute GVHD than sibling transplant recipients age ≤50 years did (hazard ratio [HR], 6.35), although this difference was not statistically significant ($P = .08$).

Control Group Comparison

The demographic and clinical characteristics of the study group (those receiving R-BEAM with bortezomib) and those of the control group (those receiving R-BEAM without bortezomib) did not differ significantly (Table 1), although patients in the study group were older and had a higher percentage of MUD transplants. The median follow-up duration was 46.5 months (range, 1.7–196.8) for all control patients and 134.3 months (range, 46.5–196.8) for control patients alive at last follow-up. For the weighted assessments, there was considerable overlap between the inverse probability weighting of the two groups. The groups' weighted cumulative incidences of grade II-IV acute GVHD (Figure 2A), grade III or IV acute GVHD (Figure 2B), and chronic GVHD (Figure 2C), as well as OS (Figure 3A), did not differ significantly. Analysis of the OS in the combined study and control groups of patients further confirmed the statistically different rates of survival based on patients age (≤50 years versus >50 years) and donor type (sibling versus MUD) described in the study group of patients (Figure 3B).

The 100-day, 1-year, and end-of-assessment NRM rates of the study group (23%, 31%, and 41%, respectively) were not statistically different from those of the control group (14%, 33%, and 50%, respectively; $P = .74$).

DISCUSSION

In this phase 1/2 study, we showed that the addition of bortezomib to the R-BEAM myeloablative conditioning regimen did not reduce the risk of acute or chronic GVHD after alloSCT in patients with lymphoid malignancies. Owing to *C. difficile* colitis, the MTD of bortezomib in this setting was 1 mg/m^2. However, we found promising survival results for patients age ≤50 years, who had a long follow-up time of 60.7 months, and for whom the median OS was not reached. This is the only prospective trial studying the combination of bortezomib plus rituximab for the prevention of GVHD after myeloablative conditioning for alloSCT.

Bortezomib-based GVHD prophylaxis without rituximab has been previously described at a different dose and schedule. Koreth et al conducted such a study in a phase 2 trial in patients undergoing myeloablative conditioning before receiving transplants from mismatched unrelated donors or MUDs [37]. The outcomes were retrospectively compared with a near-contemporaneous standard-of-care cohort (N =45) of patients who received myeloablative conditioning from 2010 to 2012, MUD with T cell-replete peripheral blood grafts and tacrolimus/methotrexate GVHD prophylaxis. Despite older patients ($P = .02$) and use of HLA-mismatched grafts ($P < .001$) in the bortezomib-based versus standard-of-care cohort, the cumulative incidence of both grades II to IV and II to IV acute GVHD appeared lower in the presence of bortezomib (38% versus 56%, $P = .04$ and 12% versus 27%, $P = .07$; respectively). One-year cumulative incidences of chronic GVHD were similar in both groups. Contrary to these findings, the present study's results did not demonstrate lower

rates of acute GVHD, NRM, and better long-term outcomes among patients who received bortezomib-based prophylaxis. Whereas most of the patients in the study by Koreth et al had acute myeloblastic leukemia, with 14 patients (41%) receiving MUD transplants and 20 (59%) receiving mismatched-unrelated or -related donor peripheral blood grafts, all of the patients in the present study received transplants from matched related or unrelated donors. Moreover, our patients received rituximab on days −13, −6, +1, and +8 and 1 mg/m^2 bortezomib on days −13, −6, −1, and +2, whereas those in the study by Koreth et al received no rituximab and 1.3 mg/m^2 bortezomib on days +1, +4, and +7. Although GVHD prophylaxis with tacrolimus and methotrexate was used in both trials, the immunosuppression taper was started at day 100 in the Koreth et al trial but started at day 180 day in our trial. These differences, together with both trials' non-randomized designs, may explain the studies' different outcomes.

The patients in the present study were heavily pretreated; in addition, 66% had PET positivity at the time of transplantation, and 21% had an HCT-specific comorbidity index of ≥3. Our results suggest that in this high-risk patient population, the R-BEAM regimen has promising therapeutic potential for patients of who are ≤ 50 years and who received sibling or MUD transplants. The median OS has not been reached in these patients. However, the survival rates of patients age >50 years who received MUD transplants were significantly lower than those of patients age ≤50 who received sibling or MUD transplants; of the 11 patients in this group, only 1 (9%) remains alive. These patients' poorer survival was likely related to their higher incidence of grade III or IV acute GVHD.

Several previous studies have suggested that bortezomib and rituximab have a synergistic effect against lymphoma in vitro. In the present study, however, the study group (R-BEAM with bortezomib) and the control group (R-BEAM without bortezomib) did not have significantly different OS after adjustment for donor type, which suggests that the addition of bortezomib to R-BEAM provides no additional OS benefit. The incidence of GVHD in these 2 trials is similar to a trial with fludarabine plus BEAM described recently by O'Meara et al [38].

The addition of bortezomib resulted in 2 of the first 3 treated patients dying from *C. difficile* infections, which prompted us to lower the bortezomib dose to 1.0 mg/m^2 and administer prophylactic metronidazole in subsequent patients. William et al reported an increased risk of *C. difficile* infection in conjunction with the addition of bortezomib to BEAM in lymphoma patients receiving autologous SCT [39]. In that study, 23% of the treated patients developed *C. difficile* colitis, with 11% developing grade 3 or higher colitis. Those findings have prompted researchers to consider the MTD of bortezomib to be 1.0 mg/m^2 for lymphoma patients receiving autologous SCT, which is in accordance with our findings. However, *C. difficile* colitis was not observed in the studies by Koreth et al, who used a conditioning regimen of busulfan and fludarabine, suggesting that this toxicity may be related to the additional innate toxicity of the BEAM regimen.

We acknowledge the limitations of the non-randomized design of our study. The importance of this concept of randomization stems from recent results of a randomized trial conducted by Koreth et al showing no benefit to the addition of bortezomib on the incidence of GVHD

in patients receiving alloSCT after NMA conditioning [40], contrary to the findings of prior phase 2 trials reported by the same authors [41]. Another limitation in our study was the small sample size, including the small number of patients who received MUDs and were <50 years. Although the OS of the latter group was not statistically different from young patients who received sibling transplants, further studies are needed to confirm these findings.

In conclusion, our data suggest that in lymphoma patients receiving alloSCT, the addition of bortezomib to the R-BEAM myeloablative conditioning regimen given with standard GVHD prophylaxis does not result in a lower cumulative incidence of clinically significant GVHD. However, the R-BEAM regimen alone may have a survival benefit in young, heavily pre-treated lymphoma patients and should be investigated further in patients who are not eligible for NMA conditioning.

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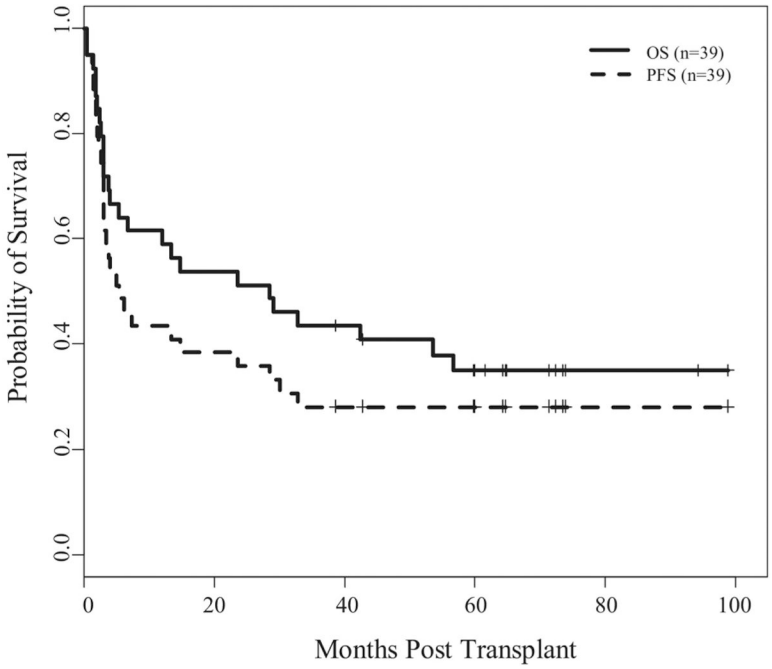

Figure 1.
OS and PFS of patients who received R-BEAM with bortezomib.

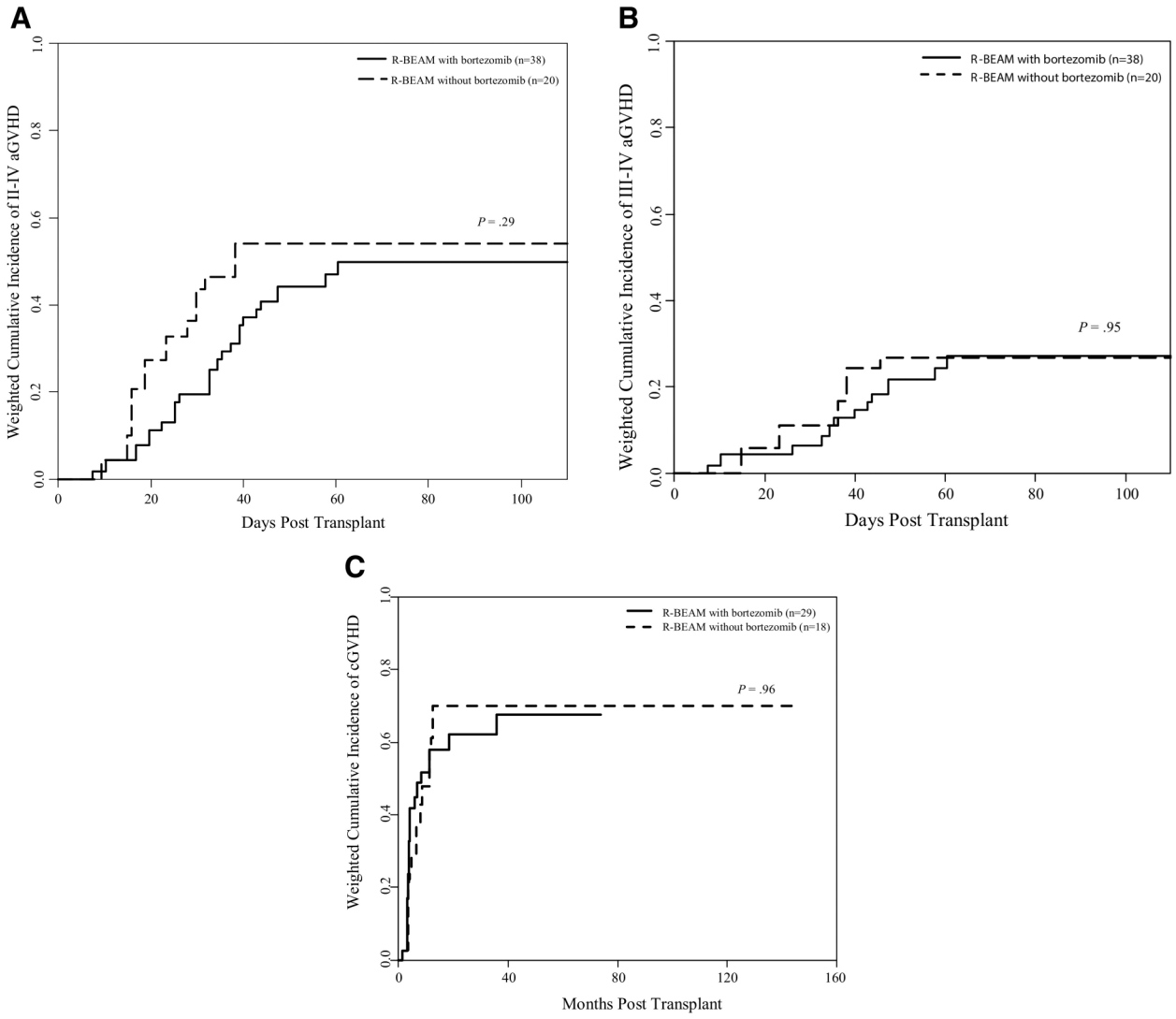

Figure 2.

(A) Weighted cumulative incidence of grade II-IV acute GVHD (aGVHD II-IV) in patients who received R-BEAM with bortezomib and those who received R-BEAM without bortezomib. (B) Weighted cumulative incidence of grade III or IV acute GVHD (aGVHD III-IV) in patients who received R-BEAM with bortezomib and those who received R-BEAM without bortezomib. (C) Weighted cumulative incidence of chronic GVHD (cGVHD) in patients who received R-BEAM with bortezomib and those who received R-BEAM without bortezomib.

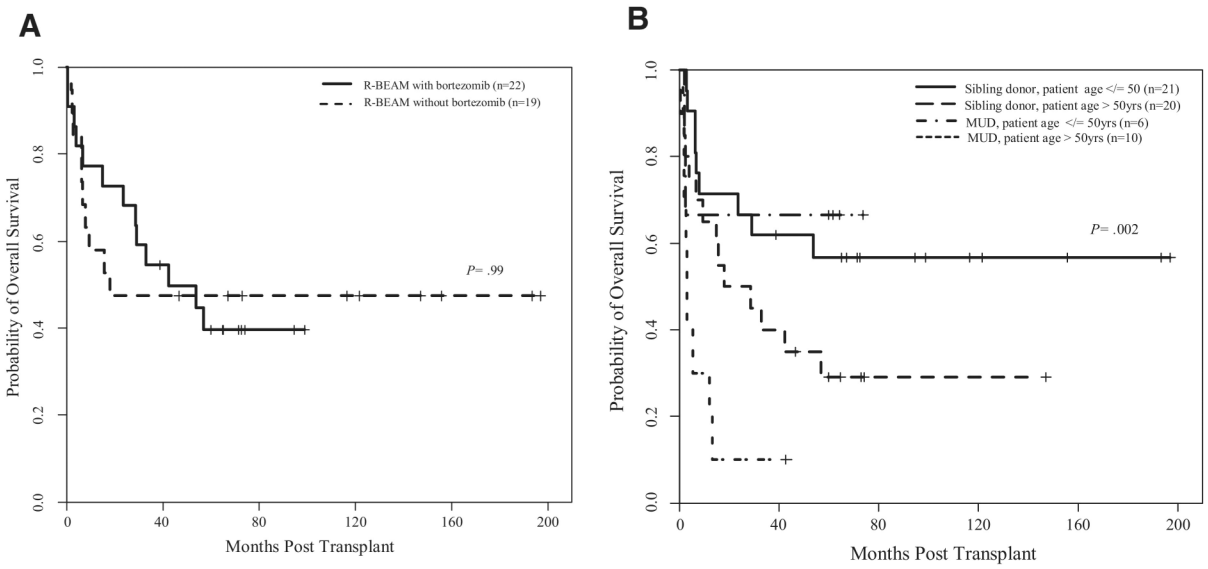

Figure 3.

(A) Weighted OS rates of patients who received R-BEAM with bortezomib and those who received R-BEAM without bortezomib. (B) OS by donor type (sibling vs. MUD) and patient age (≤50 years versus >50 years) in the combined study- and control groups. Median OS was not reached among patients age ≤50 years and who received sibling donors or who had MUDs. Patients age >50 years whose donors were MUDs had worse outcomes.

Table 1.

Clinical and transplant characteristics of allogeneic patients who received R-BEAM with or without bortezomib

Characteristic	R-BEAM with bortezomib	R-BEAM without bortezomib	*P*
No. of patients	39	21	–
Median age, y (range)	54 (22– 65)	46 (19–59)	.007
Male gender, no. (%)	30 (77)	17 (81)	1.00
Histology, no. (%)			.19
Diffuse large B-cell lymphoma	16 (41)	13 (62)	
Chronic lymphocytic leukemia/ Richter's	12 (31)	4 (19)	
T-cell lymphoma	5 (13)		
Follicular lymphoma	4 (10)	1 (5)	
Mantle cell lymphoma	2 (5)	3 (14)	
LDH level above normal	18 (46)	6 (29)	.27
Median no. of prior chemotherapies (range)	3 (1–7)	3 (1–8)	.45
Disease status at transplantation, no. (%)			1.00
Refractory	16 (41)	8 (38)	
Sensitive	23 (59)	13 (62)	
Months from diagnosis to transplant, (range)	28.0 (5.5–257.3)	21.6 (5.8–170.2)	.38
HCT-CI, median (range)	1 (0–6)	2 (0–6)	.27
≥ 3, no. (%)	8 (21)	5 (24)	.75
Donor type, no. (%)			.008
Matched related	22 (56)	19 (90)	
Matched unrelated	17 (44)	2 (10)	
Donor median age, y (range)	45 (20–70)	43 (27–64)	.86
Stem cell source, no. (%)			.28
Peripheral blood/marrow	38/1 (97/3)	19/2 (90/10)	
ABO-mismatched transplants, no. (%)	22 (56)	7 (33)	.11
Female-to-male transplants, no. (%)	6 (15)	3 (14)	1.00
Median no. of CD34+ infused, × 10^6/Kg	5.4	4.9	.18
Cytomegalovirus status, no. (%)			.56
Recipient+/donor+	12 (31)	10 (48)	
Recipient+/donor−	17 (44)	6 (29)	
Recipient−/donor+	3 (8)	2 (10)	
Recipient−/donor−	7 (18)	3 (14)	

R-BEAM, rituximab plus carmustine, etoposide, cytarabine, melphalan; y, year; LDH, lactate dehydrogenase; HCT-CI, hematopoietic cell transplant comorbidity index.

Table 2.

Univariable and multivariable analysis of OS

		Univariable analysis			Multivariable analysis		
Variable	**Median OS in months**	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age, y							
≤50	NR	*ref*					
>50	6.6	3.58	1.41, 9.08	.007			
Donor type							
Sibling	42.3	*ref*					
MUD	5.2	1.86	0.84, 4.10	.13			
Donor type/patient age, y							
Sibling / ≤ 50	NR	*ref*				*ref*	
Sibling / > 50	30.6	2.48	0.76, 8.07	.13	0.89	0.22, 3.52	.86
MUD / ≤50	NR	0.95	0.17, 5.19	.95	0.68	0.11, 4.24	.68
MUD / >50	2.9	6.46	1.88, 22.26	.003	4.18	1.09, 16.00	.037
Disease status							
Refractory	5.2	*ref*				*ref*	
Sensitive	NR	0.38	.17, .84	.016	0.38	0.13, 1.07	.07
LDH level							
Normal	56.7	*ref*				*ref*	
Elevated	3.8	2.36	1.06, 5.26	.036	1.38	0.52, 3.64	.52
Grade III-IV aGVHD							
No		*ref*					
Yes		3.91	1.71, 8.92	.001	3.66	1.49, 8.97	.005

OS, overall survival; HR, hazard ratio; CI, confidence interval; y, years; ref, reference; MUD, matched unrelated donor; NR, not reached; aGVHD, acute graft-versus-host disease.

Note: Grade III-IV aGVHD was included in the model as a time-dependent covariate.

Table 3.

Univariable and multivariable analysis of PFS

		Univariable analysis			Multivariable Analysis		
Variable	**Median PFS in months**	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Donor type/patient age, y							
Sibling / ≤ 50	18.3	*ref*			*ref*		
Sibling / > 50	21.6	1.30	0.46, 3.67	.61	.38	.11, 1.38	.14
MUD / ≤50	NR	0.87	0.22, 3.50	.85	.80	.18, 3.45	.76
MUD / >50	2.7	2.87	1.00, 8.20	.05	2.20	.72, 6.70	.16
Disease status							
Refractory	3.0	*ref*			*ref*		
Sensitive	14.7	0.46	0.22, 0.96	.040	.28	.10, 78	.015
LDH level							
Normal	28.4	*ref*			*ref*		
Elevated	3.2	2.15	1.00, 4.59	.049	1.56	.64, 3.84	.33
Grade III-IV aGVHD							
No		*ref*			*ref*		
Yes		2.93	1.30, 6.61	.010	4.03	1.57, 10.31	.004

PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; y, year; ref, reference; MUD, matched unrelated donor; NR, not reached; LDH, lactate dehydrogenase; aGVHD, acute graft-versus-host disease.

Note: Grade III-IV aGVHD was included in the model as a time-dependent covariate.

Table 4.

Non-hematologic adverse events after R-BEAM with bortezomib

Event type, no.	Grade 2	Grade 3	Grade 4 or 5
Infection	2	8	3
Gastrointestinal			
Nausea/vomiting	6	3	-
Diarrhea	2	4	-
Mucositis	2	2	
Genito-urinary	2	4	-
Neurologic	-	3	-
Pulmonary	1	-	-
Liver	1	-	1

R-BEAM, rituximab plus carmustine, etoposide, cytarabine, and melphalan.