Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT
American Society for Blood and Marrow Transplantation

Clinical Research: Adult

A Bortezomib-Based Regimen Offers Promising Survival and Graft-versus-Host Disease Prophylaxis in Myeloablative HLA-Mismatched and Unrelated Donor Transplantation: A Phase II Trial

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A B S T R A C T

Hematopoietic stem cell transplantation (HSCT) recipients lacking HLA-matched related donors have increased graft-versus-host disease (GVHD) and nonrelapse mortality (NRM). Bortezomib added to reduced-intensity conditioning can offer benefit in T cell–replete HLA-mismatched HSCT and may also benefit myeloablative conditioning (MAC) transplants. We conducted a phase II trial of short-course bortezomib plus standard tacrolimus/methotrexate after busulfan/fludarabine MAC in 34 patients with predominantly myeloid malignancies. Fourteen (41%) received 8/8 HLA-matched unrelated donor (MUD) and 20 (59%) received 7/8 HLA-mismatched related/unrelated donor peripheral blood stem cell grafts. Median age was 49 years (range, 21 to 60), and median follow-up was 25 months (range, 11 to 36). The regimen was well tolerated. No dose modifications were required. Neutrophil and platelet engraftment occurred at a median of 14 (range, 10 to 33) and 17 (range, 10 to 54) days, respectively. Median 30-day donor chimerism was 99% (range, 90 to 100), and 100-day grades II to IV and III to IV acute GVHD incidence was 32% and 12% respectively. One-year chronic GVHD incidence was 50%. Two-year cumulative incidence of both NRM and relapse was 16%. Two-year progression-free and overall survival rates were 70% and 71%, respectively. Outcomes were comparable to an 8/8 MUD MAC cohort (n = 45). Immune reconstitution was robust. Bortezomib-based MAC HSCT is well tolerated, with HLA-mismatched outcomes comparable with 8/8 MUD MAC HSCT, and is suitable for randomized evaluation. (clinicaltrials.gov: NCT01323920.)

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is potentially curative in advanced or aggressive hematologic malignancies. Whereas a sibling donor matched at HLA-A, -B, -C, and -DRB1 is optimal, only about 30% of patients who may benefit from HSCT have such a donor available [1]. The likelihood of finding a matched unrelated donor (MUD) varies between racial and ethnic groups. Accepting a 7/8 HLA match increases the likelihood of identifying an adult donor for all, from the highest likelihood group (whites of European descent [75%→97%]) to the lowest likelihood group (blacks of South or Central American descent [16%→66%]) [1], but at the expense of worse outcomes. In myeloablative conditioning (MAC) HSCT, observational studies comparing 7/8 versus 8/8 HLA MUDs document an increased rate of 100-day severe grades III to IV acute graft-versus-host disease (GVHD; 37% versus 28%) and 1- to 2-year nonrelapse mortality (NRM; 34% to 45% versus 22% to 36%), with worse progression-free survival (PFS; 38% to 41% versus 47% to 52%) and overall survival (OS; 41% to 43% versus 52% to 54%) [2-4].

The proteasome inhibitor bortezomib can selectively deplete proliferating alloreactive T lymphocytes, reduce Th1 cytokines, and block antigen presenting cell (APC) activation [5,6]. Bortezomib may also spare regulatory T cells (Tregs) that may be relevant in GVHD control [7]. Administered early after stem cell infusion, bortezomib can control GVHD in MHC-mismatched mouse HSCT and maintain therapeutic graft-versus-tumor responses [8-10] while avoiding the severe colonic toxicity that delayed or prolonged bortezomib administration can induce in mice [9].

In a previous study of T cell–replete reduced-intensity conditioning (RIC), we showed that a bortezomib-based GVHD prophylaxis regimen (days +1, +4, and +7 plus standard-of-care tacrolimus/methotrexate [tac/MTX]) appeared to be safe and efficacious in HLA-mismatched HSCT, comparable with HLA-matched transplantation [11,12]. Prospective, randomized, controlled trials of bortezomib-based T cell–replete RIC HSCT are ongoing at the national level (BMTCTN 1203). We therefore undertook a phase II trial to determine whether bortezomib-based GVHD prophylaxis is also effective with the more cytotoxic conditioning regimen intensity in MAC HSCT using matched unrelated and mismatched donors.

METHODS

This prospective, single-arm, phase II trial was approved by the institutional review board of the Dana-Farber Cancer Institute/Harvard Cancer Center (DFCI 11-007). Written informed consent was obtained before enrollment. (clinicaltrials.gov: NCT01323920.)

Trial Cohort

Participants with various hematologic malignancies aged 18 to 60 years and lacking a timely 8/8 HLA-matched (-A, -B, -C, -DRB1) related donor (MRD) received an 8/8 HLA-MUD or a 1-locus mismatched related or unrelated donor (MMRD, MMUD). Participants with HIV infection, active hepatitis B or C, abnormal renal (serum creatinine greater than the upper limit of normal, creatinine clearance < 60 mL/min) or pulmonary (forced expiratory volume in 1 second, forced vital capacity, or lung diffusing capacity for carbon monoxide < 60%) or hepatic function (serum total bilirubin greater than the upper limit of normal, serum alanine or aminotransferases more than 2 times upper limit of normal), Eastern Cooperative Oncology Group performance status > 2, uncontrolled infections, peripheral neuropathy ≥ grade 2 within 21 days before, or history of seizures were excluded. Enrollment time period was 2011 to 2012, and dataset was locked May 1, 2014.

MAC comprised fludarabine (40 mg/m^2 i.v.) and busulfan (130 mg/m^2 i.v., without pharmacokinetic (PK) dose adjustment) daily on days −7, −6, −5, and −4. Target unmanipulated peripheral blood stem cell (PBSC) dose was ≥2 × 10^6 CD34$^+$ cells/kg. GVHD prophylaxis comprised tacrolimus (starting day −3 to achieve a target serum level of 5 to 10 ng/mL), MTX (15 mg/m^2 i.v. on days +1, 10 mg/m^2 i.v. on days +3, +6, and +11), and bortezomib (1.3 mg/m^2 i.v. on days +1, +4, and +7, in accordance with the standard 72-hour bortezomib dose interval). Tacrolimus taper commenced day +100, with the goal to be off immune suppression by day +180 in the absence of GVHD.

Standard-of-Care Comparator Cohort

Clinical outcomes were also obtained for all adult hematologic malignancy patients (n = 45) undergoing off-protocol 8/8 MUD PBSC MAC HSCT at our center between 2010 and 2012 with standard-of-care tac/MTX prophylaxis dosed similar to the study cohort (tacrolimus starting day −3; MTX on days +1, +3, +6, and ±11). Tacrolimus taper routinely commenced around week 9, with the goal to be off immune suppression by 6 months in the absence of GVHD. HSCT eligibility criteria were similar to those above. MAC was composed of cyclophosphamide/total body irradiation (TBI). Target PBSC dose was ≥2 × 10^6 CD34$^+$ cells/kg. Median follow-up in survivors was 36 months (range, 13 to 49).

Supportive Care

Participants received filgrastim 5 µg/kg daily from day +12 until an absolute neutrophil count > 1000 cells/µL was attained and at least 12 months of Pneumocystis jiroveci and herpes simplex virus/varicella-zoster virus prophylaxis. Antifungal prophylaxis was not routine.

Immune Reconstitution Assays

CD4$^+$ T cells were defined as CD3$^+$CD4$^+$; CD4$^+$ naive cells were defined as CD4$^+$, CD45RO$^-$; CD4$^+$ memory cells were defined as CD4$^+$CD45RO$^+$; CD8$^+$ T cells were defined as CD3$^+$CD8$^+$; CD8$^+$ naive cells were defined as CD8$^+$CD45RO$^-$CD62L$^+$; CD8$^+$ memory cells were defined as CD8$^+$CD45RO$^+$; CD8$^+$ terminal effector cells were defined as CD8$^+$CD45RO$^-$CD62L$^-$; CD4 Tregs were defined as CD3$^+$CD4$^+$CD25$^{med-high}$CD127^{low}; natural killer (NK) cells as CD56$^+$CD3$^-$; and B cells as CD19$^+$. Fifty microliters of whole blood (15% EDTA) in 5-mL polystyrene round-bottom reaction tubes were incubated with fluorophore-conjugated monoclonal antibodies: anti-CD3 V450 (clone UCHT1; BD Biosciences, San Jose, CA), anti-CD4 APC-H7 (clone RPA-T4; BD Biosciences), anti-CD8 Pacific-Orange (clone RPA-T8; Biolegend, Dedham, MA), anti-CD25 PE-Cy7 (clone M-A251; BD Biosciences), anti-CD127 PE-Cy5 (clone eBioRDR5; eBioscience, San Diego, CA), anti-CD62L APC (clone DREG-56; BD Biosciences), CD45RO FITC (clone UCHL1; BD Biosciences) for T cell subsets; anti-CD56 PE (clone B159; BD Biosciences), anti-CD3 V450 (clone UCHT1; BD Biosciences) for NK/NKT cells; anti-CD19 APC (clone HIB19; BD Biosciences) for B cells. RBC lysis with 500 µL 1 times BD Pharm Lyse followed. Immune reconstitution flow cytometry analysis used FACSCanto II (BD Bioscience) and FACSDiva software (BD Bioscience).

Statistical Considerations

Baseline characteristics were reported descriptively. Neutrophil and platelet engraftment was the number of days to absolute neutrophil count ≥ 500 cells/µL and platelet count ≥ 20,000 cells/µL, respectively, in the absence of transfusions. Acute GVHD was graded per the consensus grading system [13].

PFS was measured from the date of stem cell infusion to disease relapse/progression or death. Patients alive without disease relapse/progression were censored at the time last seen alive and progression-free. OS was measured from the date of stem cell infusion to death from any cause. Patients alive or lost to follow-up were censored at the time last seen alive. PFS and OS were estimated by the method of Kaplan-Meier. The log-rank test was used for comparisons of Kaplan-Meier curves.

Cumulative incidence of GVHD was constructed reflecting time to relapse or death without GVHD as a competing event. Cumulative incidence of NRM and relapse with or without death were constructed reflecting time to relapse and time to nonrelapse death, respectively, as competing risks. Difference between cumulative incidence curves in the presence of a competing risk was tested using the Gray method [14]. Immunologic parameters were analyzed descriptively and compared using the exact Wilcoxon-rank-sum test.

All testing was 2-sided at the significance level of .05, and multiple comparisons were not adjusted. All calculations were done using SAS 9.3 (SAS Institute Inc, Cary, NC) and R version 2.13.2 (the Comprehensive R Archive Network project, http://www.r-project.org).

RESULTS

Study Cohort

Thirty-four participants enrolled in the phase II study. Baseline characteristics including diagnoses and disease risk index are presented in Table 1. Most participants (27, 79%) had myeloid disease. Median participant age was 49 years (range, 21 to 60). Most received mismatched grafts. Fourteen participants (41%) received 8/8 HLA MUD grafts, and 20 (59%) received 1-locus HLA-mismatched grafts (18 MMUD, 2 MMRD) (Supplemental Table 1). Median follow-up time among survivors was 25 months (range, 11 to 36).

One participant died on day 11 before engraftment. For the remainder, the median time to neutrophil and platelet engraftment time was 14 days (range, 10 to 33) and 17 days (range, 10 to 54), respectively. Total nucleated cell donor chimerism by day 30 was 99% (range, 90% to 100%) and by day 100 was also 99% (range, 73% to 100%). The regimen was well tolerated. No bortezomib doses were missed or reduced because of toxicity. No serious adverse events attributable to bortezomib (eg, neuropathy) were documented. Non-hematologic toxicities, with organ dysfunction (hepatic, renal, pulmonary) and metabolic/endocrine abnormalities, were anticipated after MAC HSCT. None experienced hepatic veno-occlusive disease.

Six participants died without evidence of disease relapse/progression, for a 2-year cumulative NRM incidence of 16%

Table 1
Baseline Characteristics of the Bortezomib Study Cohort (N = 34)

Characteristic	Mean	Range
Age, yr	49	21-60
	No. of Cases	Percent
Age ≥ 50	16	47.1
Patient sex		
Male	14	41.2
Female	20	58.8
Donor sex		
Male	19	55.9
Female	15	44.1
Male patient and female donor	4	11.8
HLA typing at -A, -B, -C, -DRB1		
8/8 MUD	14	41.2
7/8 Unrelated (MMUD)	18	52.9
Mismatch locus		
A	8	
B	1	
C	6	
DRB1	3	
7/8 Related (MMRD)	2	5.9
Mismatch locus		
A	1	
DRB1	1	
Diagnosis		
AML	17	50
CML	1	2.9
MM/PCD	1	2.9
ALL	2	5.9
MDS	6	17.6
MPD	3	8.8
NHL	4	11.8
Graft source		
PBSC	34	100
GVHD prophylaxis		
Tac/bortezomib/MTX	34	100
Patient or donor CMV seropositivity		
Yes	29	85.3
Disease risk index		
Low	1	2.94
Intermediate	24	70.59
High	9	26.47
HCT-CI		
0	15	44.1
1-2	9	26.5
≥3	10	29.4

AML indicates acute myelogenous leukemia; CML, chronic myelogenous leukemia; MM/PCD, multiple myeloma/plasma cell dyscrasia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; MPD, myeloproliferative disorder; NHL, non-Hodgkin lymphoma; CMV, cytomegalovirus; HCT-CI, hematopoietic cell transplantation–specific comorbidity index.

(Figure 1A). Three died of infection: 1 participant each with enterococcus/aspergillus infection, pneumonia/respiratory failure, and gram-negative rod/gram-positive cocci sepsis, all nonattributable to bortezomib. Five participants relapsed, for a 2-year cumulative incidence of relapse of 16% (Figure 1A). GVHD incidence was low, with 3 deaths. Grades II to IV acute GVHD occurred in 13 participants, 5 of whom experienced isolated upper gastrointestinal GVHD (gastrointestinal stage 1, overall grade II). The median time of grades II to IV acute GVHD onset was 34 days (range, 16 to 181), with a 100-day and 180-day cumulative incidence of 32% and 38%, respectively (Figure 1B); 180-day cumulative incidence of grades II to IV acute GVHD involving skin, liver, and/or lower gut was 24%. Four participants developed grades III to IV severe acute GVHD (2 had grade IV acute GVHD), for a 180-day cumulative incidence of 12%. Chronic GVHD occurred in 21 patients, with a median time to onset of 241 days (range, 110 to 807). The 1-year cumulative incidence of chronic GVHD was 50%. Of these, 18 had extensive chronic GVHD, for a 1-year

cumulative incidence of 41%. The 2-year PFS and OS rates were 70% and 71%, respectively (Figure 1C).

Comparison with MUD MAC HSCT

Trial outcomes were retrospectively compared with a near-contemporaneous standard-of-care MAC cohort (N = 45) from 2010 to 2012, receiving 8/8 MUD with T cell–replete PBSC grafts and tac/MTX GVHD prophylaxis. The cohorts were similar with regards to diagnoses, patient sex, donor–recipient sex match, cytomegalovirus serostatus, disease risk index, and hematopoietic cell transplantation–specific comorbidity index scores (Supplemental Table 2). In the standard-of-care cohort, 1 patient died before neutrophil engraftment and another died before platelet engraftment. The median time to neutrophil engraftment was 14 days (range, 11 to 60), comparable with the bortezomib-based cohort ($P = .44$), and the median time to platelet engraftment was 20 days (range, 12 to 139), possibly delayed compared with the bortezomib-based cohort ($P = .07$). 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 day 180 grades II to IV acute GVHD (38% [95% confidence interval {CI}, 22% to 54%] versus 56% [95% CI, 40% to 69%]; $P = .044$; Supplemental Figure 1) and cumulative incidence of grades III to IV severe acute GVHD (12% [95% CI, 4% to 25%] versus 27% [95% CI, 15% to 40%]; $P = .07$) appeared to be possibly lower in the presence of bortezomib. One-year cumulative incidences of chronic GVHD and 2-year NRM and relapse were similar. Importantly, 2-year PFS and OS were similar despite use of HLA-mismatched transplantation in the bortezomib-based cohort. Comparing the subset of patients who received bortezomib-based 7/8 MMUD/MMRD versus the 8/8 MUD standard-of-care MAC cohort also yielded similar outcomes (Supplemental Table 3).

Comparison of Bortezomib-MUD versus -MMUD/MMRD Cohorts

We also compared MUD versus MMUD/MMRD outcomes within the study cohort. The median time to engraft neutrophils and platelets did not differ meaningfully. Median day 30 and day 100 total nucleated cell chimerism was 98% to 99% for both groups and time points. Two-year cumulative incidence of NRM was 14% versus 15%, respectively ($P = .52$) (Figure 2A); 180-day cumulative incidence of GVHD was possibly different, with grades II to IV acute GVHD involving the skin, liver, and/or lower gut at 14% versus 30% and grades III to IV severe acute GVHD of 7% versus 15%, respectively (Figure 2B). However, this difference did not reach statistical significance ($P = .28$ and .48, respectively). One-year cumulative incidence of chronic GVHD was 57% versus 45% ($P = .40$), and extensive chronic GVHD was 43% versus 40%, respectively ($P = .74$). Overall, the HLA-matched patients did better than the mismatched patients, with a 2-year relapse incidence of 0% versus 26%, respectively ($P = .044$) (Figure 2A), a 2-year PFS rate of 86% versus 59%, respectively ($P = .03$) (Figure 2C), and a 2-year OS rate of 86% versus 61%, respectively ($P = .06$) (Figure 2D).

Immune Reconstitution

In the bortezomib-based study cohort, the median total CD3$^+$ T cell count/μL at 1, 6, and 12 months posttransplantation was 426 (Quartiles 1-3 [Q1-3], 246 to 687), 640 (Q1-3, 342 to 1135), and 643 (Q1-3, 351 to 1129), respectively (Figure 3A). The median CD20$^+$ B cell count/μL
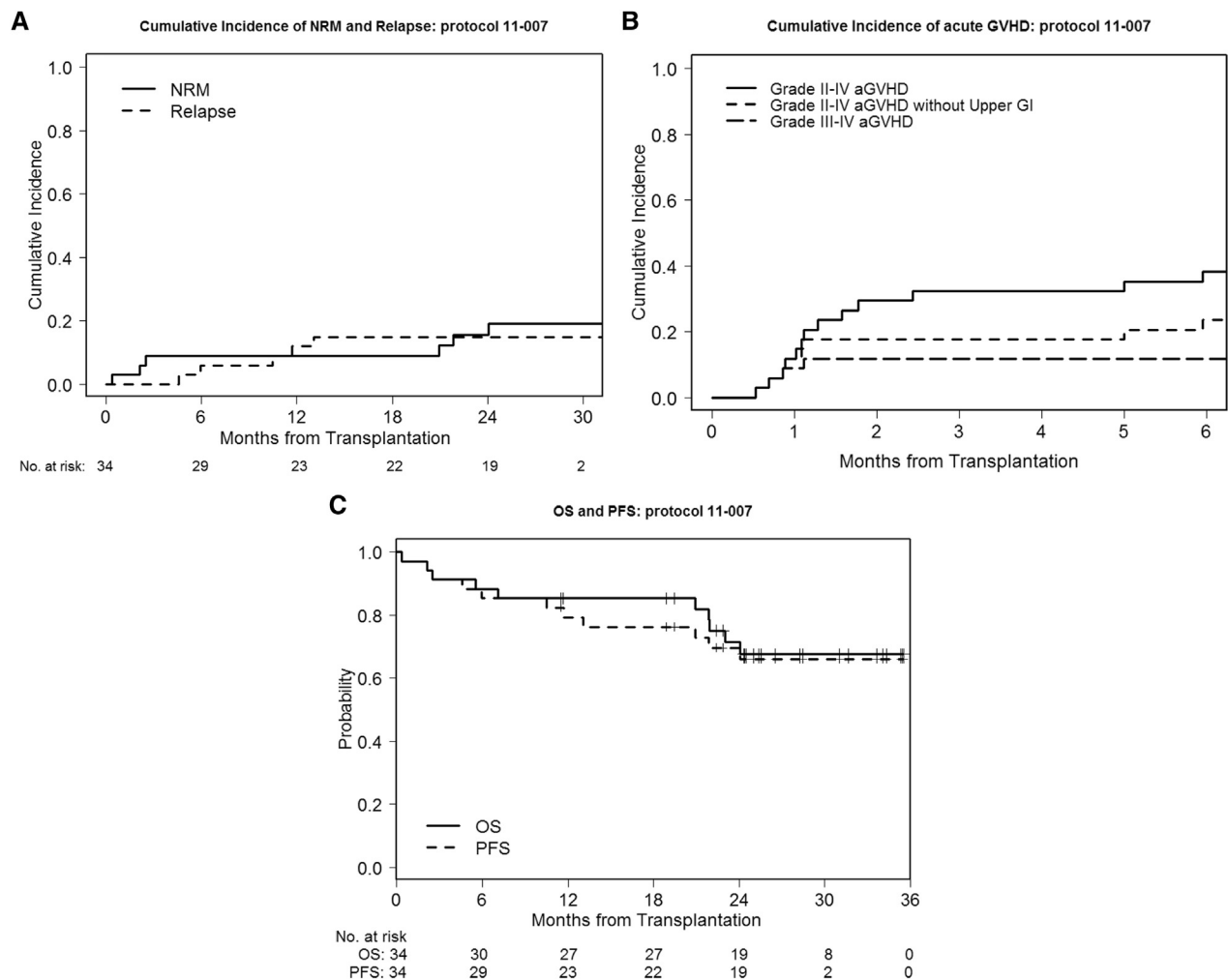
Figure 1. (A) NRM and relapse incidence of the bortezomib study cohort. (B) Grades II to IV and III to IV acute GVHD incidence of the bortezomib study cohort. (C) OS and PFS of the bortezomib study cohort.

at 1, 6, and 12 months post-transplantation was 5 (Q1-3, 2 to 11), 120 (Q1-3, 50 to 304), and 194 (Q1-3, 73 to 309), respectively Figure 3A). The median $CD56^+CD3^-$ NK cell count/μL at 1, 6, and 12 months post-transplantation was 252 (Q1-3, 193 to 371), 122 (Q1-3, 76 to 183), and 162 (Q1-3, 88 to 251), respectively (Figure 3A).

Regarding T subset reconstitution, the median total $CD8^+$ T cell count/μL at 1, 6, and 12 months post-transplantation was 144 (Q1-3, 63 to 401), 224 (Q1-3, 113 to 647), and 266 (Q1-3, 126 to 461) (Figure 3B). The median total $CD4^+$ T cell count/μL at 1, 6, and 12 months post-transplantation was 218 (Q1-3, 143 to 340), 253 (Q1-3, 215 to 376), and 333 (Q1-3, 186 to 462), respectively (Figure 3C). $CD4^+$ Treg and $CD4^+$ and $CD8^+$ naive and memory T cell reconstitution was also assessed (Figure 3B,C). Additionally, immunologic recovery did not appear to be impaired in bortezomib-MMUD/MMRD compared with bortezomib-MUD recipients (data not shown).

DISCUSSION

Most adult hematologic malignancy patients who may benefit from HSCT lack an available sibling donor and are usually transplanted from either a MUD or 1-locus HLA-mismatched donors (with umbilical cord blood and haploidentical donors also considered to be comparable). For 8/8 MUD, with improvements in DNA-based typing and supportive care, survival outcomes are similar to MRD HSCT [15,16]. However, MUD HSCT is still associated with increased acute grades II to IV (52% versus 34%) and III to IV (21% versus 16%) GVHD and NRM (relative risk, 2.76; $P < .01$) [17]. The use of 1-locus mismatched donors adds risk. A retrospective study of 2825 MAC HSCT recipients with myeloid disease predominantly grafted with bone marrow from 7/8 versus 8/8 MUD documented increased severe acute grades III to IV GVHD at 100 days (37% versus 28%; $P < .001$) and higher 1-year NRM (45% versus 36%; $P < .001$), with poorer rates of 1-year disease-free survival (38% versus 47%; $P < .001$) and OS (43% versus 52%; $P < .001$) [2]. A more recent retrospective analysis of 1360 adult acute leukemia patients receiving bone marrow or PBSC grafts from 7/8 versus 8/8 HLA-matched donors also documented increased 2-year NRM (34% to 38% versus 22% to 24%) and poorer 2-year disease-free survival for patients in remission at time of MAC HSCT (39% to 41% versus 50% to 52%) [3]. Another retrospective analysis of 2646 adult patients with various hematologic malignancies (including lymphoma and myeloma) receiving predominantly MAC transplantation with PBSC grafts from 7/8 versus 8/8 HLA-matched donors documented a higher rate of NRM ($P < .01$) and poorer rates of
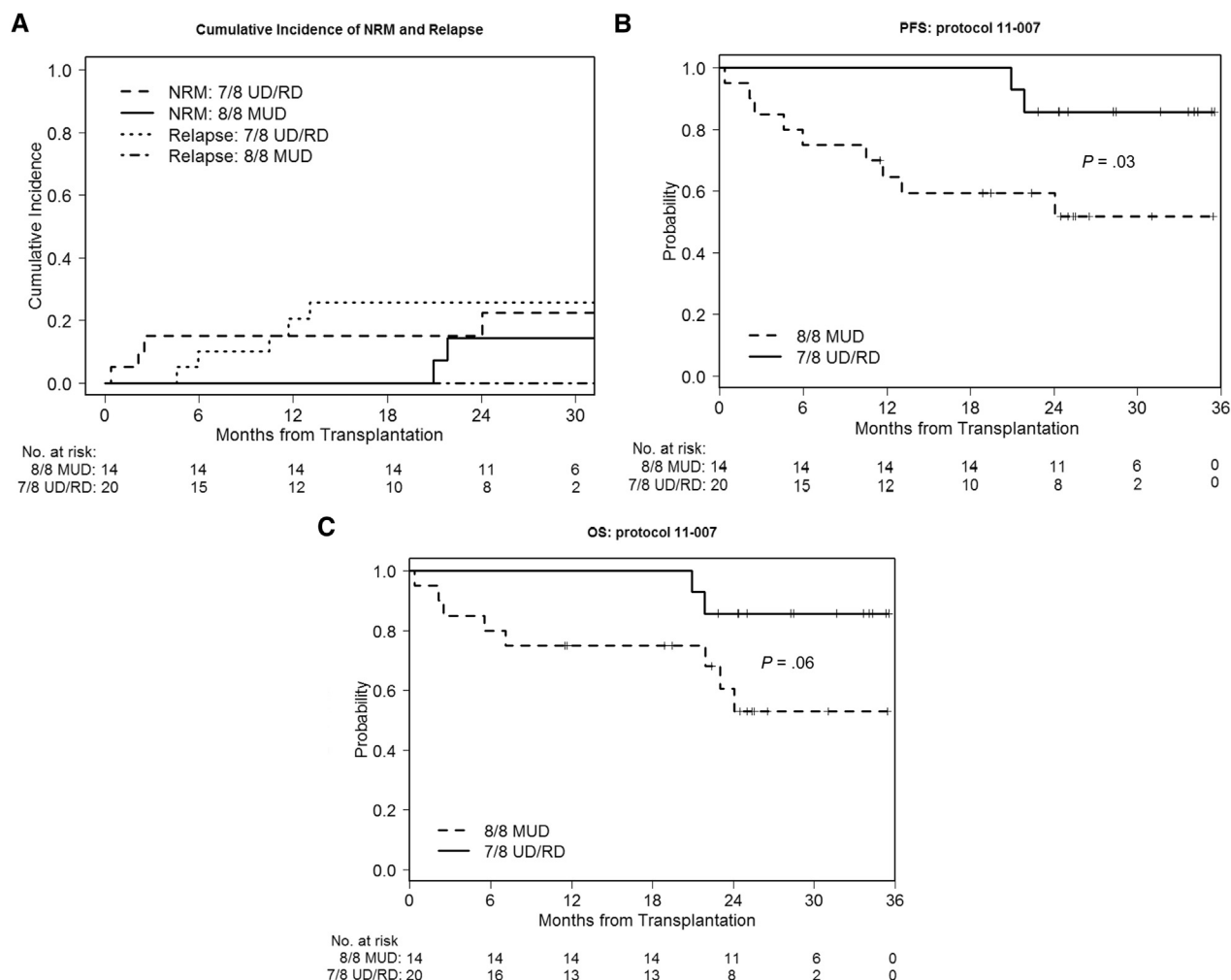
Figure 2. (A) NRM and relapse incidence of the bortezomib-MUD versus -MMUD/MMRD cohorts. (B) PFS of the bortezomib-MUD versus -MMUD/MMRD cohorts. (C) OS of the bortezomib-MUD versus -MMUD/MMRD cohorts.

OS ($P < .01$; 2-year survival rate of 41% versus 54%, respectively) [4]. These studies indicate that regardless of graft source (bone marrow, PBSC), worse outcomes are anticipated in patients lacking 8/8 HLA-matched sibling donors because of increased acute GVHD and NRM and poorer disease-free survival and OS. Novel regimens to improve outcomes for such patients would represent a major advance.

Bortezomib has immunomodulatory properties relevant to allogeneic HSCT, and based on its encouraging results in HLA-mismatched RIC HSCT, we prospectively evaluated a regimen of short-course bortezomib plus tacrolimus and MTX for MAC HSCT recipients lacking 8/8 HLA MRDs. Bortezomib, limited to 3 doses early after transplantation (days +1, +4, and +7), appears to have little systemic toxicity. No patient developed toxicities associated with more prolonged bortezomib therapy (eg, neuropathy, colonic necrosis), and no hepatic veno-occlusive disease was noted despite the lack of PK-targeted busulfan conditioning. Treatment-related toxicity after bortezomib-based MAC HSCT is in the range previously reported for HLA-matched transplantation.

The bortezomib-based MAC HSCT regimen appears to be efficacious. The 100-day cumulative incidence of grades II to IV acute GVHD was 32%, and both MUD and MMUD/MMRD

survival (rates of 2-year OS of 86% and 61%, respectively) were substantially better than anticipated compared with registry data [2-4,17]. However, retrospective registry outcomes may not represent an adequate comparator. To place our findings in context, we therefore compared the bortezomib-MUD/MMUD/MMRD cohort with a near-contemporaneous MUD MAC HSCT cohort receiving a T cell–replete PBSC graft and standard-of-care tac/MTX GVHD prophylaxis at our center. The cohort was similar to the bortezomib-based cohort in most parameters, including disease risk index and comorbidity scores. It differed with regards to systematic use of cyclophosphamide (Cy)/TBI (versus busulfan/fludarabine) MAC, whose impact, if any, remains uncertain. Although some retrospective and prospective cohort studies indicate a survival benefit of busulfan- (primarily busulfan/Cy) versus TBI-based (primarily Cy/TBI) MAC, other analyses fail to document such benefit, and a phase III randomized trial indicated impaired survival of busulfan/fludarabine (versus busulfan/Cy) MAC HSCT, suggesting that use of ablative busulfan/-fludarabine conditioning in the bortezomib-based study cohort is unlikely to provide a priori survival advantages [18-21]. We document that despite the increased patient age and HLA-mismatched donor use in the study cohort, the
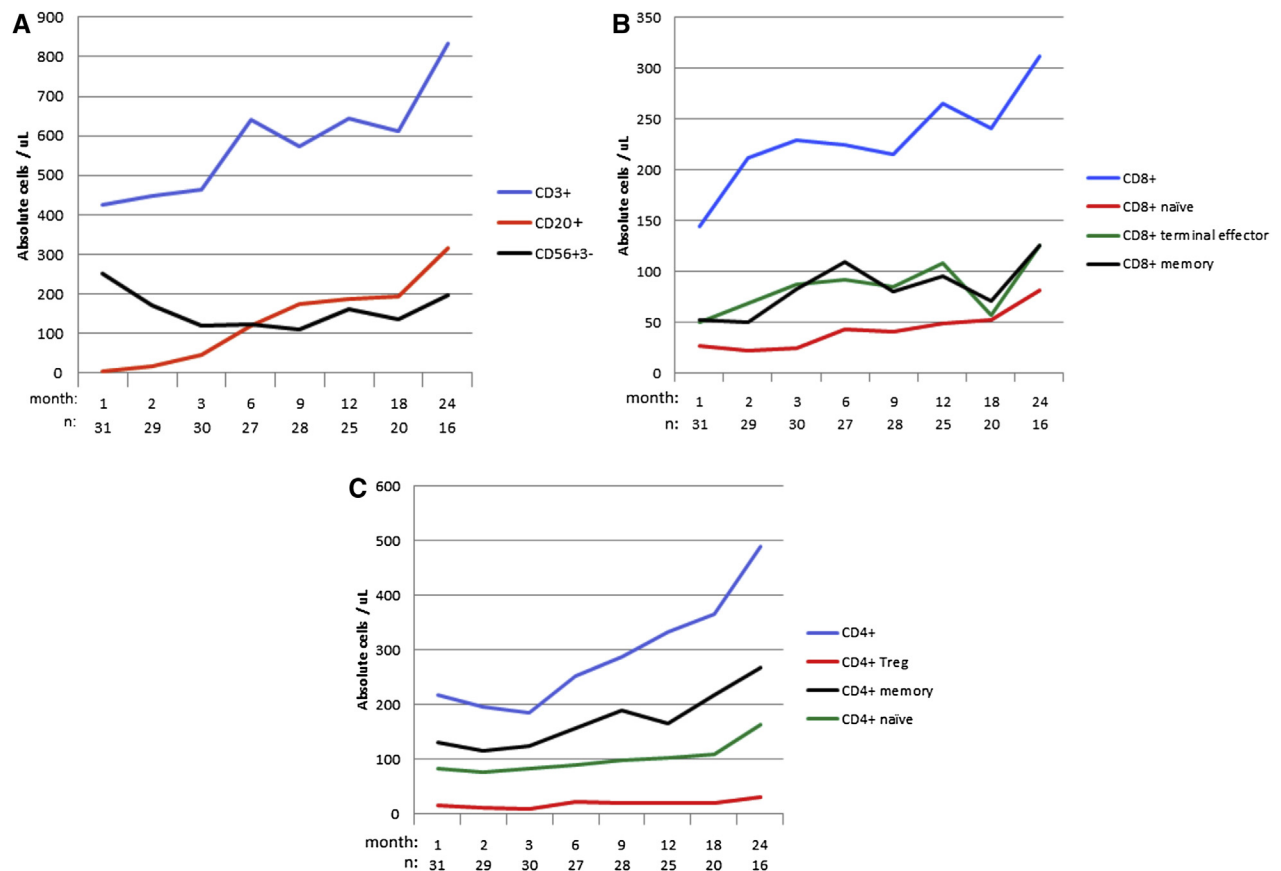
Figure 3. Immune reconstitution of the bortezomib cohort. (A) Median values of absolute CD3+ T, CD20+ B, and CD56+CD3− NK cell counts. (B) Median values of absolute CD8+, CD8+ naive, and CD8+ memory cell counts. (C) Median values of absolute CD4+, CD4+ naive, CD4+ memory, and CD4+ Treg cell counts.

bortezomib- and standard-of-care MUD MAC HSCT cohorts had similar clinical outcomes of engraftment, NRM, relapse, chronic GVHD, and survival, with a possible reduction in acute GVHD with bortezomib use. We also assessed the effect of bortezomib on immunologic reconstitution, which appeared to be robust in the study cohort.

Compared with both published retrospective analyses and institutional MUD MAC control cohorts with standard GVHD prophylaxis, outcomes of both MUD and 1-locus mismatched MAC HSCT with the addition of bortezomib appear to be promising. Although these phase II results are encouraging, we caution that such retrospective and non-randomized comparisons have inherent limitations, being subject to bias and confounding, even in apparently well-matched cohorts such as those described above. However, they are useful in a hypothesis-generating context, providing support for prospective randomized evaluation of bortezomib-based MAC HSCT.

In the myeloablative context, a short-course bortezomib-based regimen is safe, with evidence of efficacy in acute GVHD prophylaxis and with 1-locus mismatched survival comparable with 8/8 MUD HSCT. Bortezomib appears to be an active agent in MAC HSCT and is a candidate for prospective randomized evaluation.

ACKNOWLEDGMENTS

The authors thank clinical research nurses Susan Stephenson, RN, and Mildred Pasek, RN. J.K. is a Scholar in Clinical Research of the Leukemia and Lymphoma Society.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.bbmt.2015.05.027.

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