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National Marrow Donor Program–Sponsored Multicenter, Phase II Trial of HLA-Mismatched Unrelated Donor Bone Marrow Transplantation Using Post-Transplant Cyclophosphamide

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PURPOSE Hematopoietic cell transplantation (HCT) is curative for hematologic disorders, but outcomes are historically inferior when using HLA-mismatched donors. Despite unrelated donor registries listing > 38 million volunteers, 25%-80% of US patients lack an HLA-matched unrelated donor, with significant disparity across ethnic groups. We hypothesized that HCT with a mismatched unrelated donor (MMUD) using post-transplant cyclophosphamide (PTCy), a novel strategy successful in overcoming genetic disparity using mismatched related donors, would be feasible and increase access to HCT.

PATIENTS AND METHODS We performed a prospective phase II study of MMUD bone marrow HCT with PTCy for patients with hematologic malignancies. The primary end point was 1-year overall survival (OS), hypothesized to be 65% or better. 80 patients enrolled at 11 US transplant centers (December 2016-March 2019). Following myeloablative or reduced-intensity conditioning–based HCT, patients received PTCy on days +3, +4, with sirolimus and mycophenolate mofetil starting on day +5. We compared outcomes to Center for International Blood and Marrow Transplant Research contemporary controls receiving PTCy.

RESULTS Notably, 48% of patients enrolled were ethnic minorities. 39% of pairs were matched for 4-6 out of 8 HLA alleles. The primary end point was met, with 1-year OS of 76% (90% CI, 67.3 to 83.3) in the entire cohort, and 72% and 79% in the myeloablative and reduced-intensity conditioning strata, respectively. Secondary end points related to engraftment and graft-versus-host-disease were reached. Multivariate analysis comparing the study group with other mismatched HCT controls found no significant differences in OS.

CONCLUSION Our prospective study demonstrates the feasibility and effectiveness of HCT with an MMUD in the setting of PTCy. Remarkably, nearly half of the study participants belonged to an ethnic minority population, suggesting this approach may significantly expand access to HCT.

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INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is a well-established potentially curative therapy for hematologic diseases. The best outcomes are seen in the setting of a well-matched donor, historically an HLA-matched sibling, although more recently, similar outcomes are achieved using a graft from an HLA-matched (at HLA-A, -B, -C, -DRB1, or 8 out of 8 alleles) unrelated donor (URD).^{1,2} HLA-matched sibling donor availability ranges from 13% to 51%,³ and although international URD registries list > 38 million volunteer donors, a substantial proportion of patients still lack a matched URD (MUD), and patients from racial or

ethnic minorities are disproportionately disadvantaged. The National Marrow Donor Program/Be The Match (NMDP) performed an analysis with > 10.5 million URD and found the probability of identifying an MUD for a Caucasian patient of 75% compared to 19% for an African-American patient.⁴

Although HCT with a mismatched donor (MMUD) is possible, survival for these patients is historically inferior, with increased graft-versus-host disease (GVHD) and graft failure when standard calcineurin inhibitor-based GVHD prophylaxis is used.^{5,6} Addition of T-cell–depleting agents^{7,8} or ex vivo depletion of T cells effectively reduces GVHD but increases the

ASSOCIATED CONTENT

See accompanying editorial on page 1951

Appendix

Data Supplement Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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risks of other adverse outcomes such as infection, graft failure, and relapse, with the net effect of lowering survival.

A novel strategy for GVHD prevention using post-HCT high-dose cyclophosphamide (PTCy) is based on the immunobiologic rationale that recently activated, alloreactive effector T cells (responsible for GVHD) are selectively sensitive to the toxic effects of this drug and that regulatory T-cell function is preserved, avoiding more widespread immunosuppressive effects.⁹⁻¹¹ PTCy effectively overcomes the barriers associated with multiple HLA-mismatches in the mismatched related (haploidentical) donor setting, with acceptable rates of engraftment, GVHD, and survival demonstrated in several single-center and multicenter clinical trials.^{12,13} Single-center data expanding this approach to the use of MMUD showed safety and feasibility.¹⁴

The goals of our phase II prospective clinical trial were therefore twofold: first, to improve outcomes of MMUD HCT using PTCy, and second, to increase access to HCT for underserved patients, especially racial or ethnic minorities, lacking an HLA-matched donor.

PATIENTS AND METHODS

Study Design and Eligibility

This study was sponsored by the NMDP, opened at 11 centers in the United States, and was approved by the NMDP central institutional review board ($n = 2$) or the transplant center (TC) institutional review board ($n = 9$) (ClinicalTrials.gov identifier: [NCT02793544](https://clinicaltrials.gov/ct2/show/study/NCT02793544)). All patients (cases and contemporary controls) provided written informed consent.

Eligible patients were 15-71 years old; had a diagnosis of acute or chronic leukemia, myelodysplastic syndrome, or lymphoma; were eligible for a standard-of-care first allogeneic HCT using bone marrow (BM) as the stem cell source; had a Karnofsky or Lansky performance score (KPS or LPS) of $\geq 60\%$; and adequate pulmonary, renal, cardiac, and liver function. Patients were excluded if they had a suitable HLA-identical sibling or MUD available. Patients with HIV were permitted on study if additional eligibility requirements were met (Protocol, online only).

Study Treatment

All patients underwent standard pre-transplant evaluations and staging procedures. Donor searches were performed by NMDP per TC practice. The study had two non-randomized conditioning intensity strata, either myeloablative (MAC) or reduced-intensity conditioning (RIC), with the strata selected at the TC's discretion. TCs selected among three MAC regimens: cyclophosphamide and total body irradiation (TBI); busulfan and cyclophosphamide; or fludarabine and busulfan. One RIC regimen was used: fludarabine, cyclophosphamide, and low-dose TBI. Thereafter, patients received a fresh BM graft on day 0, PTCy on days +3, +4, and sirolimus and mycophenolate

mofetil starting on day +5. Supportive care was per TC policy. Relapse-prevention strategies were allowed at center discretion, although donor leukocyte infusions were not permitted before day 100.

Evaluation and Toxicity Assessments

The schedule of patient assessments is shown in the Data Supplement (online only). Clinician assessments of toxicity (National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03) were performed, and all grade 5 and unexpected grade 3 and 4 toxicities were reported. Monitoring of two key safety end points (overall mortality and grade 2-4 acute GVHD [aGVHD] by day +100) was conducted weekly, with protocol-defined triggers for study pause and data safety monitoring board review. No stopping rules were triggered. GVHD was graded and treated per institutional guidelines using standard criteria.¹⁵

Study End Point and Statistical Analysis

The primary end point of this study was 1-year overall survival (OS). Sample size was based on estimation of the 1-year OS using 90% CIs within each of two strata; a sample size of 40 patients in each stratum was expected to have a 90% CI width of 27% when the 1-year OS was 65%. Correspondingly, when the true OS percentage is 65%, there is 80% power to rule out an OS percentage of $\leq 45\%$ at $\alpha = .10$ (two-sided). Hypotheses for key secondary end points included that engraftment would be $> 90\%$ and that the incidence of grade 3-4 aGVHD would be $< 15\%$ at 100 days. Primary graft failure (PGF) was defined as lack of donor-derived neutrophil engraftment ($< 5\%$ donor chimerism) by day +56.

OS, progression-free survival, grade 3-4 aGVHD-free survival, and GVHD-free, relapse-free survival (GRFS) were estimated using the Kaplan-Meier method.¹⁶ Cumulative incidence of nonrelapse mortality (NRM), relapse, grade 2-4 aGVHD, grade 3-4 aGVHD, chronic GVHD (cGVHD), and hematologic recovery were calculated using the Aalen-Johansen estimator to account for competing risks¹⁷ of relapse for NRM and death for all other end points; 90% CI are reported for all outcomes.

We performed an unplanned analysis of comparator data, which was available from the Center for International Blood and Marrow Transplant Research (CIBMTR) registry. All patients in the United States whose data were reported to CIBMTR and underwent a first allogeneic HCT between December 2016 and March 2019 using a MMUD with a peripheral blood stem cell (PBSC) graft or a mismatched related donor with a PBSC or a BM graft, received PTCy as GVHD prophylaxis, and otherwise met eligibility criteria for the phase II clinical trial were included. All analyses used standard stepwise Cox regression modeling,¹⁸ with results expressed as hazard ratios (HR) with 95% CI. All variables studied met the assumptions for proportionality. All P values are two-sided; P values $< .05$ were considered to

TABLE 1. Baseline Characteristics for Clinical Trial Patients by Conditioning Intensity

Characteristic	MAC	RIC	Total
No. of patients	40	40	80
No. of centers	9	8	11
HIV infection pre-HCT, No. (%)			
No	40	36 (90)	76 (95)
Yes	0	4 (10)	4 (5)
Age at HCT, years, No. (%)			
Median (min-max)	48.5 (18-66)	59.5 (23-70)	51.5 (18-70)
15-29	8 (20)	3 (7.5)	11 (13.8)
30-49	13 (32.5)	11 (27.5)	24 (30)
50-70	19 (47.5)	26 (65)	45 (56.3)
Sex, No. (%)			
Male	23 (58)	19 (48)	42 (53)
Female	17 (43)	21 (53)	38 (48)
Race, No. (%)			
American Indian or Alaska Native	1 (3)	0	1 (1)
Asian	1 (3)	1 (3)	2 (3)
Black or African American	9 (23)	6 (15)	15 (19)
White	29 (73)	31 (78)	60 (75)
Not reported or unknown	0	2 (5)	2 (3)
Ethnicity, No. (%)			
Hispanic or Latino	12 (30)	7 (18)	19 (24)
Not Hispanic or Latino	28 (70)	33 (83)	61 (76)
Race or ethnicity, No. (%)			
White or non-Hispanic	17 (43)	25 (63)	42 (53)
Others	23 (58)	15 (38)	38 (48)
Karnofsky score, No. (%)			
70	2 (5)	1 (3)	3 (4)
80	12 (30)	12 (30)	24 (30)
90	21 (53)	17 (43)	38 (48)
100	5 (13)	10 (25)	15 (19)
HCT-CI, No. (%)			
0	4 (10)	9 (23)	13 (16)
1	2 (5)	8 (20)	10 (13)
2	10 (25)	4 (10)	14 (18)
3+	24 (60)	19 (48)	43 (54)
Disease status at HCT, No. (%)			
AML	23 (57.5)	14 (35)	37 (46.3)
CR1	22	10	32
CR2+	1	2	3
PIF	0	2	2
ALL	10 (25)	7 (17.5)	17 (21.3)
CR1	7	6	13
CR2+	3	1	4

(continued on following page)

TABLE 1. Baseline Characteristics for Clinical Trial Patients by Conditioning Intensity (continued)

Characteristic	MAC	RIC	Total
CLL	0	3 (7.5)	3 (3.8)
CR	0	3	3
MDS	2 (5)	0	2 (2.5)
CR	1	0	1
HI	1	0	1
Other acute leukemia	4 (10)	0	4 (5)
CR1	3	0	3
CR2+	1	0	1
NHL	1 (2.5)	11 (27.5)	12 (15)
CR1	0	5	5
CR2+	1	3	4
Relapse	0	2	2
PIF	0	1	1
HL	0	5 (12.5)	5 (6.3)
CR1	0	2	2
Relapse	0	1	1
PIF	0	2	2
Refined disease risk index, No. (%)			
Low	3 (8)	6 (15)	9 (11)
Intermediate	29 (73)	21 (53)	50 (63)
High	3 (8)	7 (18)	10 (13)
Very high	0	3 (8)	3 (4)
NA	5 (13)	3 (8)	8 (10)
CMV serostatus, No. (%)			
Negative	16 (40)	18 (45)	34 (43)
Positive	24 (60)	22 (55)	46 (58)
Time between diagnosis to HCT, No. (%)			
< 6 months	14 (35)	10 (25)	24 (30)
≥ 6 months	26 (65)	30 (75)	56 (70)
No. of prior auto HCTs, No. (%)			
0	38 (95)	37 (93)	75 (94)
1	2 (5)	3 (8)	5 (6)
Infused total nucleated cells, ×10 ⁸ /kg, median (min-max)	2.81 (0.6-520.8)	2.8 (0.76-5.8)	2.8 (0.76-520.8)
Infused CD34 + cells, ×10 ⁶ /kg, median (min-max)	2.72 (0.89-5.24)	2.2 (0.39-6.23)	2.66 (0.39-6.23)
Conditioning regimen, No. (%)			
TBI, CY, and Flu	0	40	40 (50)
Bu and Cy	3 (8)	0	3 (4)
Bu and Flu	31 (78)	0	31 (39)
TBI and Cy	6 (15)	0	6 (8)
HLA match, No. (%)			
7 out of 8	26 (65)	23 (58)	49 (61)
6 out of 8	8 (20)	11 (28)	19 (24)
5 out of 8	5 (13)	2 (5)	7 (9)
4 out of 8	1 (3)	4 (10)	5 (6)

(continued on following page)

TABLE 1. Baseline Characteristics for Clinical Trial Patients by Conditioning Intensity (continued)

Characteristic	MAC	RIC	Total
Donor age, years, No. (%)			
Median (min-max)	27 (18-56)	29 (21-44)	29 (18-56)
18-29	24 (60)	23 (58)	47 (59)
30-39	9 (23)	11 (28)	20 (25)
40-49	4 (10)	6 (15)	10 (13)
50-59	3 (8)	0	3 (4)
Donor weight, kg, median (min-max)			
	77 (55-103)	77 (52-104)	77 (52-104)
Donor sex, No. (%)			
M	20 (50)	24 (60)	44 (55)
F	20 (50)	16 (40)	36 (45)
Donor and recipient sex, No. (%)			
M-M	12 (30)	12 (30)	24 (30)
M-F	8 (20)	12 (30)	20 (25)
F-M	11 (28)	7 (18)	18 (23)
F-F	9 (23)	9 (23)	18 (23)
Donor and recipient CMV serostatus, No. (%)			
+ and +	16 (40)	13 (33)	29 (36)
+ and -	8 (20)	7 (18)	15 (19)
- and +	8 (20)	9 (23)	17 (21)
- and -	8 (20)	11 (28)	19 (24)
Donor and recipient ABO blood match, No. (%)			
Matched	20 (50)	24 (60)	44 (55)
Minor mismatch	12 (30)	5 (13)	17 (21)
Major mismatch	8 (20)	8 (20)	16 (20)
Bidirectional	0	3 (8)	3 (4)
Follow-up, months, median (min-max)			
	12 (5.4-12)	11.9 (10-12)	12 (5.4-12)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; CR, complete remission; F, female; HCT, hematopoietic cell transplantation; HCT-CI, HCT-comorbidity index; HI, hematologic improvement; HL, Hodgkin lymphoma; M, male; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; NA, not available; NHL, non-Hodgkin lymphoma; PIF, primary induction failure; RIC, reduced-intensity conditioning; TBI, total body irradiation.

indicate statistical significance for the comparator analysis. Analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

Eighty patients (including four HIV-positive patients) were enrolled between December 2016 and March 2019. Patient, donor, and transplant characteristics, divided by strata, are shown in Table 1. Most of the transplants on the MAC strata were performed for leukemia or myelodysplastic syndrome (n = 39), whereas a significant number (n = 16) received an HCT for lymphoma or Hodgkin disease on the RIC strata. The median age of patients differed by strata (MAC = 49; RIC = 60). A large proportion of patients had high-risk features before HCT, including 54% with an HCT-CI score of ≥ 3 (MAC = 60%; RIC = 48%) and 34% with a

KPS < 90 (MAC = 35%; RIC = 33%). Of note, 48% of patients were from racial or ethnic minority groups (MAC = 58%; RIC = 38%). The average donor age was 29 years (range, 18-56 years), and 39% of patients received a graft that was mismatched for > 1 HLA allele. Total nucleated cell and CD34+ counts infused were 2.8×10^8 (range, 0.76-520.8) and 2.66×10^6 (0.39-6.23) per kg of recipient body weight, respectively.

Study End Points and Toxicity

The study achieved its primary end point with 1-year OS of 76% (90% CI, 67.3 to 83.3) in the entire cohort; survival was 72% (90% CI, 59.9 to 83.1) and 79% (90% CI, 66.9 to 88.8) in the MAC and RIC strata, respectively (Fig 1). OS did not differ by HLA match grade; in 7 out of 8 matched pairs, this was 75% (90% CI, 63.4 to 84.3) and in 4-6 out of 8, it was 77% (90% CI, 64.1 to 88.4).

Engraftment. There were no cases of PGF in the MAC strata, whereas the incidence of PGF was 7.5% (< 5% donor chimerism in whole blood) in the RIC strata.

GVHD. Patients receiving MAC had grade 2-4 and 3-4 aGVHD rates at day +100 of 43% and 18%, respectively, with cGVHD at 1 year of 36%. Patients receiving RIC had grade 2-4 and 3-4 aGVHD rates at day +100 of 33% and 0%, respectively, with cGVHD at 1 year of 18% (Table 2, Figs 2 and 3).

NRM and relapse. In MAC, NRM and relapse at 1 year were 8% and 30%, respectively, whereas in RIC, these were 10% and 23%, respectively (Table 2, Fig 4).

Toxicity. Cumulative rates of clinically meaningful viral infection (ie, those with end-organ damage or requiring treatment) were \leq 11% at 1 year (Table 2), except for BK virus (27% in MAC and 30% in RIC), adenovirus (13% in RIC) and human herpesvirus 6 (HHV6) (13% in MAC). The most common cause of death was disease relapse. Three patients died of infections (none of which were viral), and all other deaths were related to organ toxicity (Appendix Table A1, online only). Of four patients with HIV, three were transplanted with lymphoma, one of whom is alive and two of whom died because of lymphoma relapse or progression; the fourth patient, transplanted for acute leukemia, died of a fungal infection. Eleven serious unexpected events were reported in four patients; the data safety monitoring board determined that eight were possibly related, one unlikely to be related, and two unrelated to the trial procedures.

Although not protocol-specified end points, two novel composite HCT end points were assessed. GRFS (events including grade 3-4 aGVHD, cGVHD requiring systemic treatment, relapse, and death) at 1 year was 38% and 55% in the MAC and RIC strata, respectively. Grade 3-4 aGVHD-free survival at 6 months was 68% and 88% in the MAC and RIC strata, respectively.

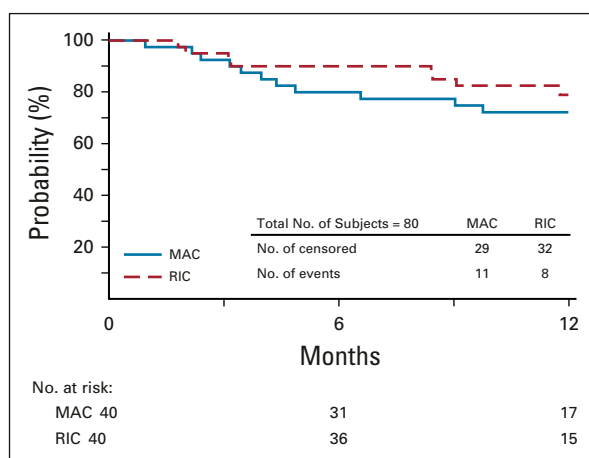


FIG 1. OS, stratified by conditioning intensity. MAC, myeloablative conditioning; OS, overall survival; RIC, reduced-intensity conditioning.

Comparison to Contemporaneous Real-World Data Collected by the CIBMTR Registry

Three cohorts of contemporary registry controls were studied: MMUD receiving PBSC grafts (n = 143), mismatched related donor recipients receiving BM grafts (n = 398), or PBSC grafts (n = 1,191). In multivariate analysis, OS at 1 year was not significantly different between the four groups ($P = .761$) (Appendix Table A2, online only). Use of older donors (> 35 years old) was associated with higher mortality in the RIC setting (HR, 1.43; CI, 1.10 to 1.84; $P = .006$) (Appendix Table A2). Data on additional characteristics and end points are in the Data Supplement.

DISCUSSION

The results from this prospective phase II multicenter clinical trial confirm the feasibility of HCT from an MMUD using PTCy, with 1-year OS of > 70%. If confirmed in larger studies, this greatly extends the donor options for patients in need of HCT, particularly those from ethnically diverse backgrounds.

The results in our RIC strata are comparable to those reported in the single-center trial,¹⁴ with a 33% incidence of grade 2-4 aGVHD (no grade 3 or 4) and 18% cGVHD (no severe cGVHD). Patients on the MAC strata experienced higher rates of aGVHD compared with our RIC strata, however without GVHD-related mortality. MAC has been associated with a higher risk of GVHD compared to RIC.¹⁹ In addition, baseline characteristics differed somewhat between the MAC and RIC strata. Patients receiving MAC were more likely to be from racial or ethnic minorities and had more pre-HCT comorbidities, both factors associated with higher risks of GVHD.^{20,21} Strategies (untested in the MMUD setting) to reduce GVHD may be the addition of antithymocyte globulin²² or altering the timing of immunosuppressive drugs.²³

We added sirolimus and mycophenolate mofetil to PTCy for GVHD prophylaxis, as in Kasamon et al.¹⁴ Sirolimus, a mechanistic target of rapamycin inhibitor, was selected in preference to the more commonly used calcineurin inhibitor (CNI), tacrolimus, because of synergism with PTCy seen in preclinical studies²⁴; however, recent data in the mismatched related setting suggest similar outcomes with either sirolimus or tacrolimus.²⁵

Abatacept, a selective inhibitor of T-cell costimulation, has also shown promise in minimally MMUD (7 out of 8 matched) HCTs, although studying this agent in the setting of multiple HLA mismatches is required. A phase II study in 43 patients receiving MMUD grafts and a CNI plus methotrexate showed grade 3-4 aGVHD at day +100 of 2.3% (patients received RIC [N = 10] or MAC [N = 33]).²⁶ Seven additional patients transplanted for sickle cell disease with an MMUD, in a phase I multicenter study, received abatacept and CNI plus methotrexate. Grade 3-4 aGVHD at day +100 was 7%. Strategies to facilitate the use of MMUDs (either related²⁷ or unrelated) in this disease are

TABLE 2. Univariate Outcomes for Clinical Trial Patients by Conditioning Intensity

Outcomes	MAC (N = 40)		RIC (N = 40)	
	No.	Prob. (90% CI)	No.	Prob. (90% CI)
OS	40		40	
6 months		80 (68.7 to 89.3)		90 (80.9 to 96.4)
1 year		72.3 (59.9 to 83.1)		78.9 (66.9 to 88.8)
NRM	40		40	
100 days		5 (0.9 to 12.2)		7.5 (2.1 to 15.8)
1 year		7.5 (2.1 to 15.8)		10 (3.6 to 19.2)
Relapse	40		40	
6 months		22.6 (12.6 to 34.5)		20 (10.6 to 31.5)
1 year		30.4 (18.9 to 43.2)		22.5 (12.6 to 34.3)
PFS	40		40	
6 months		69.9 (57.4 to 81.1)		72.5 (60.3 to 83.2)
1 year		62.1 (49.2 to 74.3)		67.5 (54.9 to 79)
Grade 2-4 aGVHD	40		40	
100 days		42.5 (29.8 to 55.7)		32.5 (20.9 to 45.3)
6 months		47.5 (34.5 to 60.7)		35 (23.1 to 48)
Grade 3-4 aGVHD	40		40	
100 days		17.5 (8.7 to 28.5)		0
6 months		20 (10.6 to 31.5)		2.5 (0.1 to 8.2)
Grade 3-4 aGVHD-free survival	40		40	
100 days		75 (63 to 85.3)		90 (80.9 to 96.4)
6 months		67.5 (54.9 to 79)		87.5 (77.7 to 94.7)
cGVHD	40		40	
6 months		27.6 (16.7 to 40.2)		10 (3.6 to 19.2)
1 year		35.5 (23.3 to 48.7)		17.5 (8.7 to 28.5)
Severe cGVHD	40		40	
6 months		5 (0.9 to 12.3)		0
1 year		7.6 (2.1 to 16)		0
GRFS	40		40	
6 months		45 (32.4 to 58)		62.5 (49.6 to 74.5)
1 year		37.5 (25.5 to 50.4)		55 (42 to 67.6)
Neutrophil recovery	40		40	
100 days		97.5 (89.7 to 100)		97.5 (89.8 to 100)
Median (range), days		17 (14 to 28)		18 (14 to 36)
Platelet recovery	40		40	
100 days		87.5 (77 to 95.1)		95 (86.2 to 99.5)
Median (range), days		33 (9 to 107)		35 (21 to 73)
Primary graft failure	39		40	
Percentage at day 56		0 (0 to 9)		7.5 (1.6 to 20.4) ^a
Grade 2-3 CMV reactivation or infection	40		40	
100 days		10.4 (3.8 to 19.8)		7.6 (2.2 to 16)
1 year		10.4 (3.8 to 19.8)		7.6 (2.2 to 16)

(continued on following page)

TABLE 2. Univariate Outcomes for Clinical Trial Patients by Conditioning Intensity (continued)

Outcomes	MAC (N = 40)		RIC (N = 40)	
	No.	Prob. (90% CI)	No.	Prob. (90% CI)
Grade 3 CMV infection	40		40	
100 days		0		2.6 (0.1 to 8.5)
1 year		0		2.6 (0.1 to 8.5)
Grade 2-3 EBV infection	40		40	
100 days		0		0
1 year		2.9 (0.1 to 9.5)		0
Grade 2 BK virus infection	38		37	
100 days		26.7 (15.7 to 39.2)		29.7 (18.3 to 42.7)
1 year		26.7 (15.7 to 39.2)		29.7 (18.3 to 42.7)
Grade 2-3 adenovirus infection	39		36	
100 days		2.6 (0.1 to 8.5)		0
1 year		9 (2.6 to 18.9)		12.6 (4.6 to 23.8)
Grade 2 HHV-6 infection	40		39	
100 days		12.5 (5.3 to 22.3)		5.1 (0.9 to 12.4)
1 year		12.5 (5.3 to 22.3)		5.1 (0.9 to 12.4)

Abbreviations: aGVHD, acute GVHD; cGVHD, chronic GVHD; CMV, cytomegalovirus; EBV, Epstein-Barr virus; GRFS, GVHD- or relapse-free survival; GVHD, graft-versus-host disease; HHV, human herpesvirus; MAC, myeloablative conditioning; NRM, nonrelapse mortality; OS, overall survival; PFS, progression-free survival; RIC, reduced-intensity conditioning.

^aN = 3 patients reported whole blood donor chimerism < 5% by day 56.

particularly relevant as some family members are excluded because of being affected by the disease, as well as paucity of MUD.²⁸

As in early studies testing PTCy in the mismatched related setting, we used BM exclusively because of the higher incidence of GVHD associated with the use of PBSC.²⁹ More

recently, several investigators have switched the graft source from BM to PBSC in the PTCy setting³⁰ because of concerns for higher disease relapse rates in aggressive disease,^{31,32} an increased incidence of graft failure,²⁹ and the lower rates of GVHD in general in the PTCy setting³³ (compared with standard GVHD prophylaxis).³⁴ Despite the increase in cGVHD, PBSC has become the graft source of choice in most HCT settings,³⁵ because of the concerns listed above, as well as the more predictable quality and ease of access of PBSC. Some studies using PTCy now report that the use of PBSC is associated with similar rates of aGVHD, and other outcomes, compared with BM,³⁶ and this will be prospectively studied in our upcoming clinical trial.

Initial results in the mismatched related PTCy setting showed a higher-than-expected incidence of disease relapse,¹³ although this was not consistently shown in later studies.³⁴ Relapse rates remain an issue to be addressed. In our study, those receiving MAC had the highest risk of disease relapse, perhaps reflecting the risk of the underlying disease (more patients with leukemia were transplanted with MAC). This may be mitigated by the use of PBSC, particularly for patients with high-risk disease.

Few studies have systematically collected and reported data on viral infections, making the data collected in our study difficult to interpret in the context of similar transplant approaches. The incidence of significant life-threatening viral infections (eg, cytomegalovirus and Epstein-Barr virus) was low, and no deaths in study participants were attributed

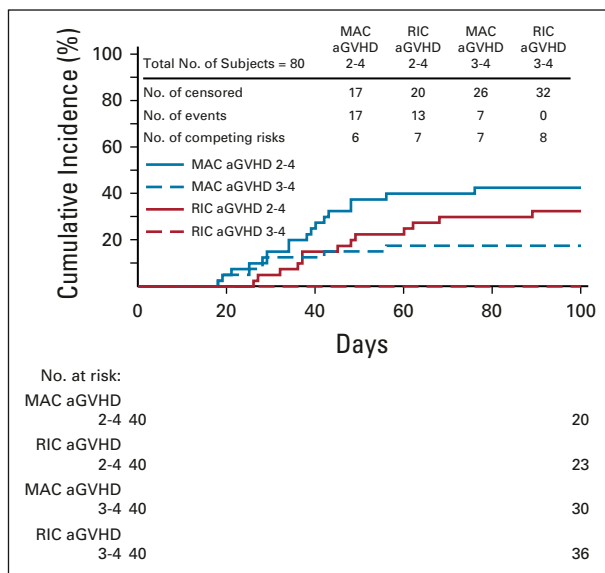


FIG 2. aGVHD by strata. aGVHD, acute graft-versus-host disease; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning.

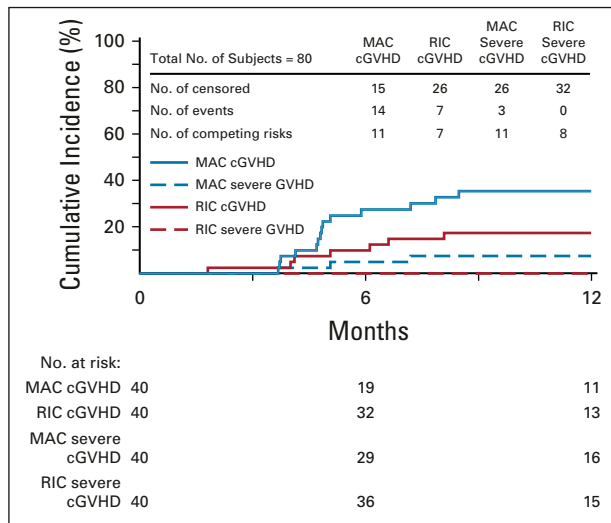


FIG 3. cGVHD by strata. cGVHD, chronic graft-versus-host disease; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning.

to a viral infection. Virtual absence of post-transplant lymphoproliferative disease with PTCy has been previously noted.³⁷ Rates of BK infection were relatively high, which warrants further investigation.

An important finding in this study is that 48% of the patients enrolled were from racial or ethnic minorities. Such patients have long faced poorer outcomes because of inequalities in access to HCT,^{38,39} greater likelihood of being transplanted with a mismatched graft,³⁸ and low enrollment into clinical trials.^{40,41} Registry modeling has shown that simply increasing the number of minority volunteer donors cannot completely close the access gap (M. Maiers, personal communication, October 2020); thus, strategies, such as the use of PTCy, to improve outcomes when using MMUDs are urgently needed. NMDP data show that when an 8 out

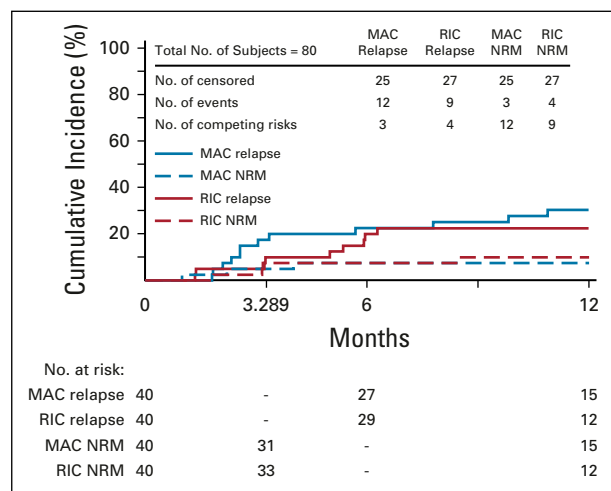


FIG 4. Relapse or NRM by strata. MAC, myeloablative conditioning; NRM, nonrelapse mortality; RIC, reduced-intensity conditioning.

of 8 MUD is not available, a 7 out of 8 MMUD can be identified for 53% of African-American patients, and expanding the match grade to < 7 out of 8 would result in an identified donor for every patient (M. Maiers, personal communication, October 2020). Thirty-nine percent of patients in our study received cells from a donor matched for < 7 out of 8 HLA alleles, and no significant difference based on the degree of disparity was found. Although the numbers in our study are too small to be definitive, this warrants further study. Indeed, there are data in the mismatched related PTCy setting suggesting that greater degrees of HLA disparity may be associated with better outcomes.⁴²

A recent article in this Journal,⁴³ publishing the ASCO Recommendations for Promoting Health Equity, includes several recommendations to facilitate equitable access to research. In her editorial, Dr Pierce, ASCO President, states “We should not rest until the opportunity to participate in clinical trials is available to—and represents—all patients with cancer, not just the 5% who enroll today.”^{44(p3361)} Our study included a remarkable number of patients from racial or ethnic minorities, which compares favorably to clinical trials in hematologic diseases and HCT and indicates the willingness of people from ethnic minorities to participate in research that address issues of importance to them.⁴⁵ A recent review of randomized controlled trials in patients with multiple myeloma, a disease which disproportionately affects black people,⁴⁰ found enrollment of 13%-21% of patients representing racial minorities. The Blood and Marrow Transplantation Clinical Trial Network, a National Institutes of Health–funded clinical trial network addressing important questions in HCT, reports between 8% and 37% racial or ethnic minority patients enrolled on its studies.⁴⁶

This study clearly shows that MMUD transplants are feasible, safe, and effective, with results similar to the results of mismatched related HCT (although the comparison to the CIBMTR data should be treated with caution as this analysis was unplanned and does not represent prospectively randomly assigned patients). The small numbers preclude assessment of many important questions that remain to be answered in future studies, including random assignment between donor types addressing the impact of stem cell source, disease, and conditioning regimen, as well as factors that may favor use of one donor type over the other. Important factors favoring mismatched related donors may include speed of graft provision and cost. Factors favoring MMUD may include the ability to select a younger donor,⁴⁷ or a donor better matched with respect to virologic serostatus and ABO blood type.³⁴ Selection of younger donors (whether mismatched related or unrelated) was associated with significantly better OS, as well as several other end points, in our comparator analysis. Donor-specific antibodies, a significant issue in the mismatched related setting (associated with increased graft failure),⁴⁸ can be completely avoided in the MMUD setting. Finally,

selection of donors with rare genetic polymorphisms can be prioritized. We included HIV-positive patients in our study and prioritized selection of CCR5-Δ32 homozygous donors, as CCR5-Δ32 homozygous donors have been associated with cure of HIV following HCT.⁴⁹ A suitable donor (ie, one who was CCR5-Δ32 homozygous) could be identified for all four patients, comparing favorably to the probability of 30% or less in the MUD setting.⁵⁰

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DISCLAIMER

The views expressed in this article do not reflect the official policy or position of the National Institutes of Health, the Department of the Navy, the Department of Defense, Health Resources and Services Administration or any other agency of the US Government.

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In conclusion, this phase II prospective clinical trial using MMUDs in the setting of PTCy showed excellent survival, acceptable rates of GVHD, and enrolled high numbers of patients from racial or ethnic minority groups. Limitations related to the use of BM, sirolimus, and the best RIC option are the focus of our upcoming study, and future research must address strategies to incorporate predictors for GVHD⁵¹ and to mitigate relapse.

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The Center for International Blood and Marrow Transplant Research (CIBMTR) supports accessibility of research in accord with the National Institutes of Health Data Sharing Policy and the National Cancer Institute Cancer Moonshot Public Access and Data Sharing Policy. The CIBMTR only releases deidentified data sets that comply with all relevant global regulations regarding privacy and confidentiality.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**National Marrow Donor Program–Sponsored Multicenter, Phase II Trial of HLA-Mismatched Unrelated Donor Bone Marrow Transplantation Using Post-Transplant Cyclophosphamide**

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APPENDIX

TABLE A1. Primary Cause of Death by 1 Year for Clinical Trial Patients

Death (N = 19)	MAC (n = 11)	RIC (n = 8)
Recurrence or progress of disease	4	3
ARDS	1	0
VOD or SOS	1	0
Pulmonary failure	2	0
Multiple organ failure	2	2
Bacterial infection	1	1
Fungal infection	0	1
Infection, organism not identified	0	1

Abbreviations: ARDS, acute respiratory distress syndrome; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; SOS, sinusoidal obstruction syndrome; VOD, veno-occlusive disease.

TABLE A2. Multivariate Analysis of OS Comparing the Clinical Trial Patients to the CIBMTR Comparator Groups

Variable	Level	Frequency	HR	HR Lower CL	HR Upper CL	P
MAC						
Donor and graft type	Overall					.700
	MMUD (BM)	40	1.00			
	MMUD (PB)	62	0.66	0.29	1.49	.317
	Haplo (BM)	141	0.69	0.34	1.40	.308
	Haplo (PB)	541	0.79	0.42	1.47	.457
Age, years	Overall					.000
	15-29	211	1.00			
	30-49	270	1.25	0.80	1.97	.326
	50+	303	2.48	1.65	3.72	.000
DRI	Overall					.011
	Low	59	1.00			
	Intermediate	496	1.40	0.71	2.77	.334
	High or very high	164	2.25	1.10	4.60	.027
	Unknown or NA	65	2.37	1.04	5.39	.040
RIC						
Donor and graft type	Overall					.761
	MMUD (BM)	40	1.00			
	MMUD (PB)	81	1.42	0.63	3.18	.393
	Haplo (BM)	257	1.23	0.59	2.59	.577
	Haplo (PB)	650	1.16	0.57	2.37	.686

(continued on following page)

TABLE A2. Multivariate Analysis of OS Comparing the Clinical Trial Patients to the CIBMTR Comparator Groups (continued)

Variable	Level	Frequency	HR	HR Lower CL	HR Upper CL	P
Age, years	Overall					.001
	15-29	62	1.00			
	30-49	200	3.67	1.31	10.3	.014
	50-59	255	4.19	1.51	11.7	.006
	60+	511	5.60	2.06	15.2	.001
Donor age, years	Overall					.006
	≤ 35	559	1.00			
	> 35	469	1.43	1.10	1.84	.006
DRI	Overall					.000
	Low	99	1.00			
	Intermediate	633	1.24	0.73	2.13	.424
	High or very high	230	2.23	1.28	3.88	.005
	Unknown or NA	66	2.02	1.03	3.97	.040
HCT-CI	Overall					.003
	0	221	1.00			
	1-2	327	1.13	0.76	1.69	.536
	3+	480	1.68	1.17	2.41	.005
KPS	Overall					.041
	90-100	569	1.00			
	< 90	459	1.30	1.01	1.67	.041

NOTE. Analyses were performed separately for MAC and RIC HCT. The main variable of interest was the donor or graft type group (each control group compared separately to the trial cohort of MMUD BM). Other variables considered in the Cox regression models using stepwise variable selection were patient age, race or ethnicity, KPS, HCT-CI, DRI, recipient CMV status, interval from diagnosis to HCT, donor-recipient sex matching, and number of prior autologous HCT (RIC strata). The main effect (donor/graft type) and variables of statistical significance are indicated in bold.

Abbreviations: BM, bone marrow; CIBMTR, Center for International Blood and Marrow Transplant Research; CL, confidence limit; CMV, cytomegalovirus; DRI, disease risk index; HCT-CI, hematopoietic cell transplantation-comorbidity index; HR, hazard ratio; KPS, Karnofsky performance score; MAC, myeloablative conditioning; MMUD, mismatched unrelated donor; NA, not available; OS, overall survival; PB, peripheral blood; RIC, reduced-intensity conditioning.