Post-Transplant Cyclophosphamide for Graft vs Host Disease Prophylaxis in Multiple Myeloma Patients Who Underwent Allogeneic Hematopoietic Cell Transplantation: First Comparison by Donor Type: A Study from the Chronic Malignancies Working Party of the EBMT.

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Post-Transplantation Cyclophosphamide for Graft-versus- Host Disease Prophylaxis in Multiple Myeloma Patients Who Underwent Allogeneic Hematopoietic Cell Transplantation: First Comparison by Donor Type. A Study from the Chronic Malignancies Working Party of the European Society for Blood and Marrow Transplantation

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A B S T R A C T

Graft-versus-host disease (GVHD) remains among the major causes of treatment failure in patients with multiple myeloma (MM) undergoing allogeneic hematopoietic cell transplantation (allo-HCT). The use of post-transplantation cyclophosphamide (PT-Cy) is now a well-established and widely used method for GVHD prophylaxis after HLA haploidentical HCT. However, the rationale for using PT-Cy in the setting of matched donor transplantation is less apparent, given the lesser degree of bidirectional alloreactivity. In this retrospective study, we investigated

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the role of PT-Cy as GVHD prophylaxis in patients with multiple myeloma underoing allo-HCT, among different donor types, to determine cumulative incidence of acute and chronic GVHD and impact on engraftment, progression-free survival (PFS), GVHD-free/relapse- free survival (GRFS), overall survival (OS), and NRM A total of 295 patients with MM underwent allo-HCT using grafts from a matched related donor (MRD; n = 67), matched unrelated donor (MUD; n = 72), mismatched related or unrelated donor (MMRD/MMUD, 1 antigen; n = 27), or haploidentical donor (haplo; n = 129) using PT-Cy between 2012 and 2018. In addition to PT-Cy, agents used in GVHD prophylaxis included calcineurin inhibitors in 239 patients (81%), with mycophenolate mofetil in 184 of those 239 (77%). For grade II-IV acute GVHD, the cumulative incidence at day +100 was 30% (95% confidence interval [CI], 25% to 36%), 9% (95% CI, 5% to 12%) for grade III-IV acute GVHD, and 27% (95% CI, 21% to 32%) for chronic GVHD (limited, 21%; extensive, 6%), with no differences by donor type. The median time to neutrophil engraftment was 19d (95% CI, 18-19), with no significant difference by donor type. The median time to platelet engraftment was delayed in haploidentical donor graft recipients (27 days versus 21 days; $P < .001$). Two-year OS, PFS, GRFS, and NRM were 51% (95% CI, 45% to 58%), 26% (95% CI, 20% to 32%), 24% (95% CI, 18% to 30%), and 19% (95% CI, 14% to 24%), respectively, with no significant difference between different donor types. In multivariable analyses, compared with the haplo donors, the use of MRDs was associated with significantly better OS (hazard ratio [HR], 0.6; 95% CI, 0.38 to 0.95; $P = .029$), and the use of MUDs was associated with a significantly higher GRFS (HR, 0.63; 95% CI, 0.42 to 0.97; $P = .034$). There was a trend toward improved PFS with use of MUDs (HR, 0.69; 95% CI, 0.46 to 1.04; $P = .08$). Our data show that PT-Cy in MM patients undergoing allo-HCT resulted in low rates of acute and chronic GVHD and led to favorable survival, especially in the matched related donor setting.

INTRODUCTION

Outcomes for patients with recurrent multiple myeloma (MM) have improved significantly over the past 2 decades with the advent of new targeted therapies and immune therapy-based strategies, such as monoclonal antibodies. Further improvement is expected with introduction of antibody-drug conjugates (ADCs), chimeric antigen receptor (CAR) T cells, and bispecific T cell engagers [1–3]. Thus far, allogeneic hematopoietic cell transplantation (allo-HCT), the original immune-based therapy, has been a potentially curative therapy in this disease, as indicated by long-term survival data [4,5] via an immune-mediated graft-versus-myeloma (GVM) effect [6].

The role of upfront allo-HCT in MM is more controversial based on randomized clinical trials. However, a recent long-term pooled analysis of 4 trials reported a benefit from tandem autologous (auto)-allo-HCT in patients with MM, supporting a durable GVM effect [4]. Salvage allo-HCT for recurrent MM is more accepted and continues to be used in appropriately selected patients [7].

Graft-versus-host disease (GVHD), nonrelapse mortality (NRM), and relapse are among major causes of treatment failure in patients with MM undergoing allo-HCT. The reported cumulative incidence of acute GVHD is in the range of 44% to 50% (grade III-IV, 8% to 18%) and that of chronic GVHD is in the range of 46% to 50% (limited, 21%; extensive, 26%) using standard prophylaxis with calcineurin inhibitors (CNIs), mycophenolate mofetil (MMF), and/or methotrexate, and that of NRM is 15% to 30% [5,7-10]. Any substantial progress in reducing severe acute and chronic GVHD may translate to less morbidity and better outcomes in patients with MM undergoing allo-HCT.

The use of post-transplantation cyclophosphamide (PT-Cy) is now a well-established and widely used method for GVHD prophylaxis after HLA-haploidentical (haplo) HCT [11-14]. In the setting of haplo-HCT, PT-Cy eliminates the rapidly proliferating alloreactive T cells bidirectionally while preserving the slowly dividing memory and regulatory T cells, resulting in comparatively less GVHD, less graft rejection, and improved immune reconstitution and ultimately promoting encouraging outcomes in haplo-HCT recipients [15,16].

Data from this approach in the setting of HLA-matched related donor (MRD), matched unrelated donor (MUD), and mismatched related or unrelated donor (MMRD/MMUD) allo-HCT are emerging [17,18]. The rationale for using PT-Cy in the setting of matched donor transplantation is less apparent, given the lesser degree of bidirectional alloreactivity. Interestingly, several retrospective analyses of PT-Cy in treating acute leukemias have reported comparatively lower rates of acute and chronic GVHD in the context of MRD and MUD allo-HCT [17–21]; however, such data are lacking in MM allo-HCT recipients.

We hypothesized that the use of PT-Cy after allo-HCT may reduce the risk of severe acute and chronic GVHD and potentially improve outcomes of patients with MM, especially in the matched donor setting. We conducted this retrospective analysis of PT-Cy as GVHD prophylaxis on MM patients undergoing allo-HCT using MRDs, MUDs, MMRDs/MMUDs (1 antigen mismatch), and haplo donors (≥2 antigen mismatches) at European Society for Blood and Marrow Transplantation (EBMT) centers and examined its impact by donor type.

METHODS

Study Design

This retrospective registry-based study was performed on behalf of the Chronic Malignancy Working Party (CMWP) of the EBMT. The EBMT registry is a voluntary group of more than 600 transplantation centers in Europe reporting all consecutive HCTs and follow-up data annually. Patients with a diagnosis of MM who underwent allo-HCT with an MRD, a 10/10 MUD, a haploidentical donor (≥2 antigen mismatches within HLA-A, -B, -C, -DRB1, and -DQB1 loci), or an MMRD/MMUD (1 antigen mismatch within HLA-A, -B, -C, -DRB1, and -DQB1 loci) and who received PT-Cy were selected. Patients with plasma cell leukemia were excluded from the study. Patients who had received ATG in combination with PT-Cy were excluded from this analysis. The study was approved by the EBMT CMWP Institutional Review Board and conducted in accordance with the Declaration of Helsinki, using Good Clinical Practice guidelines. All patients or legal guardians provided written informed consent authorizing the use of their clinical information for research purposes. The objective of this study was to evaluate the cumulative incidence of acute and chronic GVHD, engraftment, progression-free survival (PFS), GVHD- free/relapse-free survival (GRFS), and overall survival (OS), as well as NRM by 2 years, using PT-Cy as GVHD prophylaxis, among recipients of allo-HCT using the 4 different donor types.

Statistics

OS and PFS were estimated using the Kaplan-Meier product limit estimation method, and differences in subgroups were assessed by the log-rank test. The median duration of follow-up was determined using the reverse Kaplan-Meier method. The cumulative incidences of relapse and NRM were analyzed together in a competing-risks framework. Neutrophil engraftment was defined as an absolute neutrophil count $\geq 0.5 \times 10^9$/L for 3 consecutive

Table 1
Patient and Donor Characteristics and Transplantation Modalities

Characteristic		Value
KPS, n (%)		
	90-100	164 (58.4)
	<90	117 (41.6)
	Missing	14
Donor type, n (%)		
	MRD	67 (22.7)
	MUD	72 (24.4)
	Haplo	129 (43.7)
	MMRD + MMUD	27 (9.2)
GVHD prophylaxis, n (%)		
	PT-Cy + CNI	239/295 (81% of total)
	+ CNI and MMF	184/239 (77)
	+ CNI without MMF	55/239 (23)
	PT-Cy + others	56/295 (19)
Conditioning intensity, n (%)		
	MAC	102 (34.6)
	Reduced	193 (65.4)
Conditioning regimen, n (%)		
	Non-TBI	175 (60.3)
	TBI	115 (39.7)
	Missing	5
	Alkylator-based	194 (68.6)
	Non-alkylator-based	89 (31.4)
	Missing	12
Age at HCT, yr, median (IQR)	55 (49.8-66)	
Patient sex, n (%)		
	Male	173 (58.6)
	Female	122 (41.4)
Donor-patient sex match, n (%)		
	Female-male	57 (19.3)
	Other	238 (80.7)
Disease state at allo-HCT, n (%)		
	CR/VGPR	130 (45%)
	PR	91 (31.5%)
	<PR	68 (23.5%)
	Missing	6
Time between diagnosis and HCT, mo, median (IQR)	34.9 (21.2-55.6)	
Lines of therapy between auto- HCT and allo-HCT, n (%)		
	1	93 (56.7)
	2	40 (24.4)
	≥3	31 (18.9)
	Missing	131
Previous auto-HCT, n/N (%)		
	Yes	285 (96.6)
	1	182/285 (63.9)
	2	94/285 (33.0)
	3	9/285 (3.2)
	No	10 (3.4)
Allo-HCT as line of therapy, n (%)		
	Second line	196 (73)
	>Second line	43 (16)
	Upfront allo	10 (3.7)
	Upfront auto-allo	19 (7.1)
	Missing	27
Stem cell source, n (%)		
	Bone marrow	61 (20.7)
	Peripheral blood	234 (79.3)
Ig subtype, n (%)		
	IgG	142 (49.1)
	IgA	45 (15.6)
	Light chain	88 (30.4)
	Others	14 (4.8)
	Missing	6

days. The cumulative incidence of neutrophil engraftment was determined at day +28 post-allo-HCT. Platelet reconstitution was defined as an absolute platelet count $\geq 20 \times 10^9$/L for 3 consecutive days without transfusion. Competing-risks analyses were also applied to estimate the incidences of acute grade II-IV GVHD by day +100 and limited and extensive chronic GVHD at 1 year and 2 years, respectively. The competing events were relapse and death. Subgroup differences in cumulative incidence were assessed using Gray's test.

Multivariable Cox regression was applied to investigate the simultaneous impact of multiple covariates on outcomes when sufficient numbers of patients and subsequent events were available. For OS and PFS, hazard ratios (HRs) are provided. Included covariates were donor type (MRD, MUD, MMRD/MMUD versus haplo), patient age at allo-HCT (by decade), disease state at allo-HCT (partial response [PR], <PR versus complete response [CR]/very good PR [VGPR]), MM classification (IgG versus any others), conditioning intensity (reduced-intensity conditioning [RIC] versus myeloablative conditioning [MAC]), donor-recipient sex match (female to male versus any other), time from diagnosis to allo-HCT (in years), and Karnofsky Performance Status (KPS) (90 to 100 versus <90).

Continuous variables are presented as median and interquartile range (IQR), and categorical variables are presented as percentage within the group of patients with available data. All survival estimates and HRs are reported with corresponding 95% confidence intervals (CIs) in parentheses. All *P* values were 2-sided, and $P < .05$ was considered to indicate statistical significance. Statistical analyses were performed in R version 3.6.0 (R Development Core Team, Vienna, Austria), using the 'survival,' 'prodlim,' and 'cmprsk' packages.

RESULTS

Patient and Transplantation Characteristics

Between 2012 and 2018, a total of 295 patients with MM received PT-CY as GVHD prophylaxis. Patient and transplantation characteristics are summarized in Tables 1 and 2. Donor type distribution was as follows: MRD, 22.7% (n = 67); MUD 24.4% (n = 72); MMRD/MMUD, 9.2% (n = 27); haplo, 43.7% (n = 129). The GVHD prophylaxis regimen included PT-Cy in combination with a CNI, cyclosporin, or tacrolimus (n = 239 of 295; 81%), with MMF (n = 184 of 239; 77%), or without MMF (n = 55 of 239; 23%). PT-Cy plus other agents were also used (n = 56; 19%). Conditioning regimens included RIC (n = 193; 65.4%) and standard MAC (n = 102; 34.6%). Transplantation was from a female donor to a male recipient in 57 cases (19.3%) and with other combinations in 238 cases (80.7%).

The median patient age at the time of allo-HCT was 55 years (IQR, 49.8 to 66 years). The study cohort included 173 males (58.6%) and 122 females (41.4%). MM subtypes were IgG (n = 142; 49.1%), IgA (n = 45; 15.6%), light chain (n = 88; 30.4%), and other (n = 14; 4.8%). The KPS score was 90 to 100 in 164 patients (58.4%) and <90 in 117 patients (41.6%). Data on cytogenetic/fluorescence in situ hybridization abnormalities were not available.

All but 10 patients (3.4%) had undergone previous auto-HCT (n = 285; 96.6%), at a median time of 34.9 months (IQR, 21.2 to 55.6 months) before their current allo-HCT. Ninety-

Table 2
Patient Characteristics by Donor Type

Variable		Haplo (N = 129)	MRD (N = 67)	MUD (N = 72)	MMRD + MMUD (N = 27)	*P* Value
GVHD prophylaxis, n (%)						
	+ Cyclosporine/tacrolimus + MMF	118 (91.5)	23 (34.3)	25 (34.7)	18 (66.7)	<.001
	+ Cyclosporine/tacrolimus - MMF	6 (4.7)	20 (29.9)	25 (34.7)	4 (14.8)	
	+ Other	5 (3.9)	24 (35.8)	22 (30.6)	5 (18.5)	
Conditioning intensity, n (%)						
	MAC	41 (31.8)	21 (31.3)	29 (40.3)	11 (40.7)	.524
	RIC	88 (68.2)	46 (68.7)	43 (59.7)	16 (59.3)	
Conditioning regimen, n (%)						
	Non-TBI	73 (57.5)	42 (63.6)	38 (53.5)	22 (84.6)	.036
	TBI	54 (42.5)	24 (36.4)	33 (46.5)	4 (15.4)	
	Missing	2	1	1	1	
	Alkylator-based	81 (62.8)	50 (76.9)	41 (66.1)	22 (81.5)	.095
	Non-alkylator-based	48 (37.2)	15 (23.1)	21 (33.9)	5 (18.5)	
	Missing		2	10		
Age at HCT, yr, median (IQR)		55.1 (50.1-61.1)	54.8 (49.3-58.7)	56 (51.5-62.5)	52.1 (48.5-57.3)	.246
KPS, n (%)						
	<90	43 (34.7)	29 (46)	32 (47.1)	13 (50.0)	.208
	90-100	81 (65.3)	34 (54)	36 (52.9)	13 (50.0)	
	Missing	5	4	4	1	
Patient sex, n (%)						
	Male	74 (57.4)	44 (65.7)	44 (61.1)	11 (40.7)	.158
	Female	55 (42.6)	23 (34.3)	28 (38.9)	16 (59.3)	
Donor-patient sex match, n (%)						
	F->M	30 (23.3)	15 (22.4)	11 (15.3)	1 (3.7)	.083
	Other	99 (76.7)	52 (77.6)	61 (84.7)	26 (96.3)	
Disease state at allo-HCT, n (%)						
	CR/VGPR	58 (46)	27 (41.5)	32 (45.1)	13 (48.1)	.432
	PR	32 (25.4)	25 (38.5)	26 (36.6)	8 (29.6)	
	<PR	36 (28.6)	13 (20)	13 (18.3)	6 (22.2)	
	Missing	3	2	1	0	
Time between diagnosis and HCT, mo, median (IQR)		37.7 (23.1-61.5)	30.7 (20.6-53.9)	32.7 (20.6-51.5)	31.6 (19.7-57.6)	.495
Lines of therapy between auto-HCT and allo-HCT, n (%)						
	1	29 (48.3)	30 (75)	27 (52.9)	7 (53.8)	.052
	2	14 (23.3)	5 (12.5)	16 (31.4)	5 (38.5)	
	≥3	17 (28.3)	5 (12.5)	8 (15.7)	1 (7.7)	
	Missing	69	27	21	14	
Allo-HCT as line of therapy, n (%)						
	Upfront allo	10 (8.3)	0 (0)	0 (0)	0 (0)	.016
	Upfront auto-allo	12 (10)	2 (3.3)	3 (4.7)	2 (8.3)	
	Second line	78 (65)	51 (85)	51 (79.7)	16 (66.7)	
	>Second line	20 (16.7)	7 (11.7)	10 (15.6)	6 (25)	
	Missing	9	7	8	3	
Previous auto-HCT, n (%)						
	No	10 (7.8)				.004
	Yes	119 (92.2)	67 (100)	72 (100)	27 (100)	
Stem cell source, n (%)						
	Bone marrow	50 (38.8)	7 (10.4)		4 (14.8)	<.001
	Peripheral blood	79 (61.2)	60 (89.6)	72 (100)	23 (85.2)	
Ig subtype, n (%)						
	IgG	55 (44.7)	32 (47.8)	44 (61.1)	11 (40.7)	.01
	IgA	12 (9.8)	15 (22.4)	9 (12.5)	9 (33.3)	
	Light chain	48 (39)	16 (23.9)	17 (23.6)	7 (25.9)	
	Others	8 (6.5)	4 (6)	2 (2.8)	0 (0)	
	Missing	6				

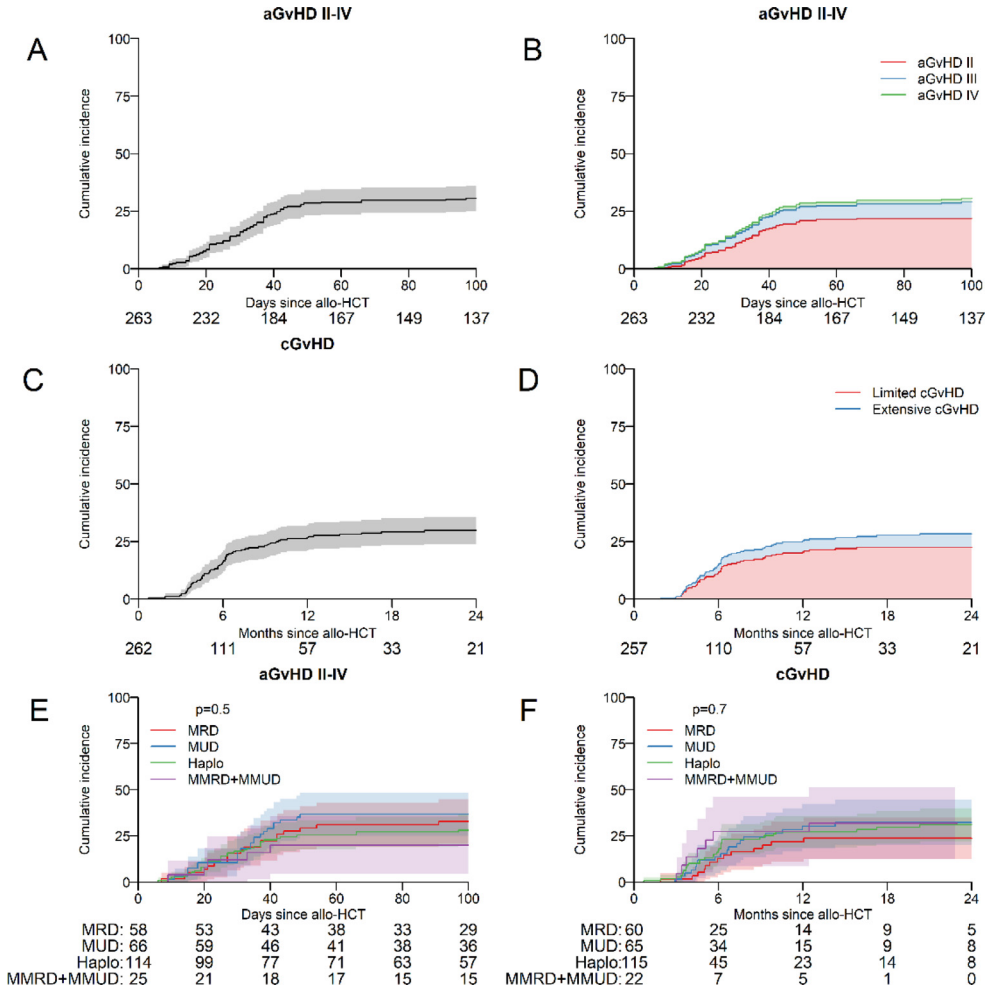

Figure 1. Cumulative incidence of acute and chronic GVHD. (A) Acute GVHD grade II-IV. (B) Acute GVHD by grade (II, III, or IV). (C) Chronic GVHD. (D) Chronic GVHD by severity (limited or extensive). (E) Acute GVHD by donor type (MRD, MUD, MMRD/MMUD, haplo). (F) Chronic GVHD by donor type (MRD, MUD, MMRD/MMUD, haplo).

four patients (33%) had undergone 2 prior auto-HCTs. Among the patients with available data, 93 (56.7%) had received 1 previous line of therapy, 40 (24.4%) had received 2 lines, and 31 (18.9%) had received ≥3 lines after previous auto-HCT and before allo-HCT, and data were not available for 131 patients. Given the amount of missing data, we analyzed the available data on allo-HCT as salvage therapy. A total of 196 patients (73%) underwent allo-HCT as second-line salvage, 43 (16%) underwent allo-HCT as third- or subsequent-line salvage, and 10 (3.7%) underwent allo-HCT upfront, without previous auto-HCT. Additionally, 19 patients (7.1%) had upfront auto-allo HCT, and data were missing in 27 patients (9.2%). The median time for starting salvage therapy for relapse/progressive disease after first HCT (for the available 164 patients) was 13.2 months (range, 0.99 to 70.6 months; IQR, 7 to 23 months), indicating that these patients represent a high-risk subgroup with early relapse. Disease status at allo-HCT was CR/VGPR in 130 patients (45%), PR in 91 (31.5%), and less than PR in 68 (23.5%). Stem cell sources were bone marrow in 61 patients (20.7%) and peripheral blood in 234 (79.3%).

Analysis stratified by donor type showed that more patents in the haplo group received therapy with CNI and MMF (n = 118; 91.5%) compared with those in the MRD (n = 23; 34.3%), MUD (n = 25; 34.7%), and MMRD/MMUD (n = 18; 66.7%) groups ($P < .001$). A CNI without MMF was given in more patients in the MRD (n = 20; 29.9%) and MUD (n = 25; 34.7%) groups compared with the haplo (n = 6; 4.7%) and MMRD/MMUD (n = 4; 14.8%) groups ($P < .001$). Additionally, more patients in the haplo group had bone marrow as the stem cell source for allo-HCT (n = 50; 38.8%) compared with the MRD (n = 7; 10.4%), MUD (n = 0), and MMRD/MMUD (n = 4; 14.8%) groups ($P < .001$). All patients had undergone previous auto-HCT except for 10 patients in the haplo allo-HCT group, who underwent allo-HCT as first line therapy ($P = .004$). More patients in the haplo group (n = 22) had also undergone allo-HCT as first-line therapy. However, the interval from diagnosis was similar across the 4 groups (haplo, 37.7 months; MRD, 30.7 months; MUD, 32.7 months; MMRD/MMUD, 31.6 months; $P = .5$). There were no statistically significant differences in age, sex, disease state at allo-HCT, conditioning intensity (MAC/RIC), MM subtype, or year of allo-HCT by donor type (Table 2). Forty-eight patients received a donor lymphocyte infusion (DLI); of these, 25 received a preemptive DLI, and data are missing for 4 patients.

Engraftment, Response, GVHD, and Survival

The cumulative incidence of neutrophil engraftment was 91% (95% CI, 88% to 95%) by day +28, at a median time to engraftment of 19 days (95% CI, 18 to 19 days) for all patients, with no significant difference by donor type on univariate

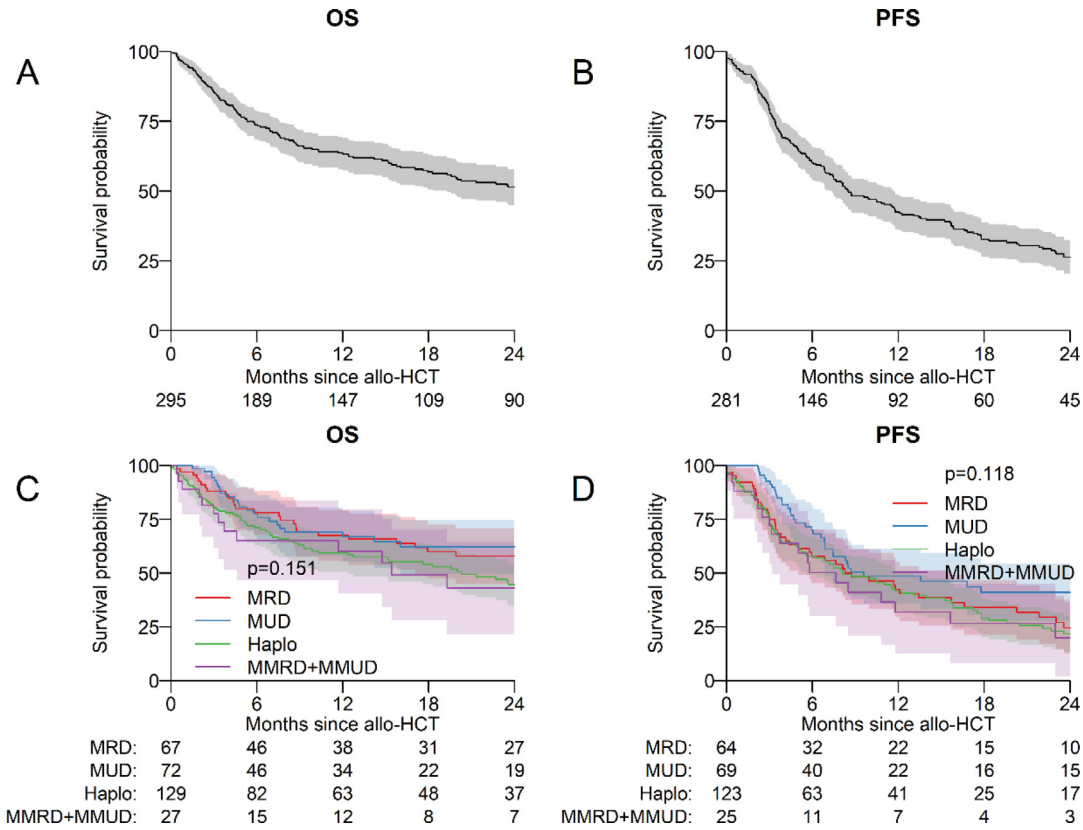

Figure 2. OS (A), PFS (B), OS by donor type (C), and PFS by donor type (D).

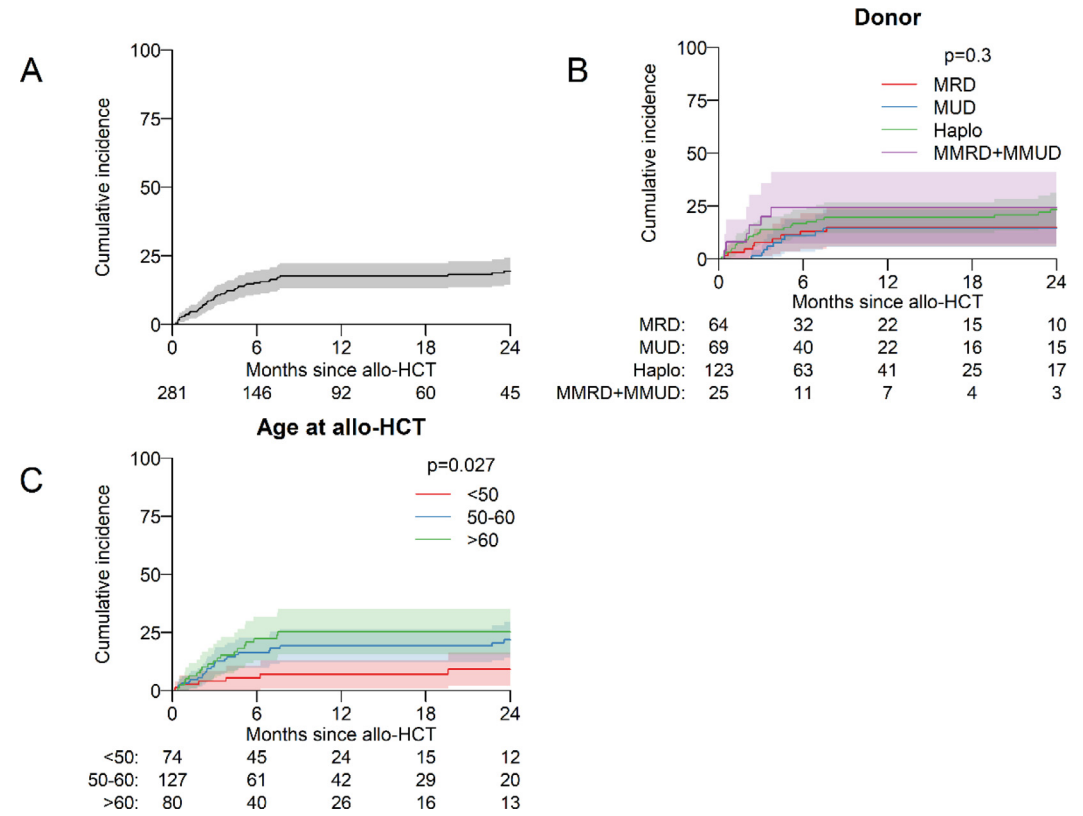

Figure 3. NRM in all patients (A), by donor type (B), and by age (C).

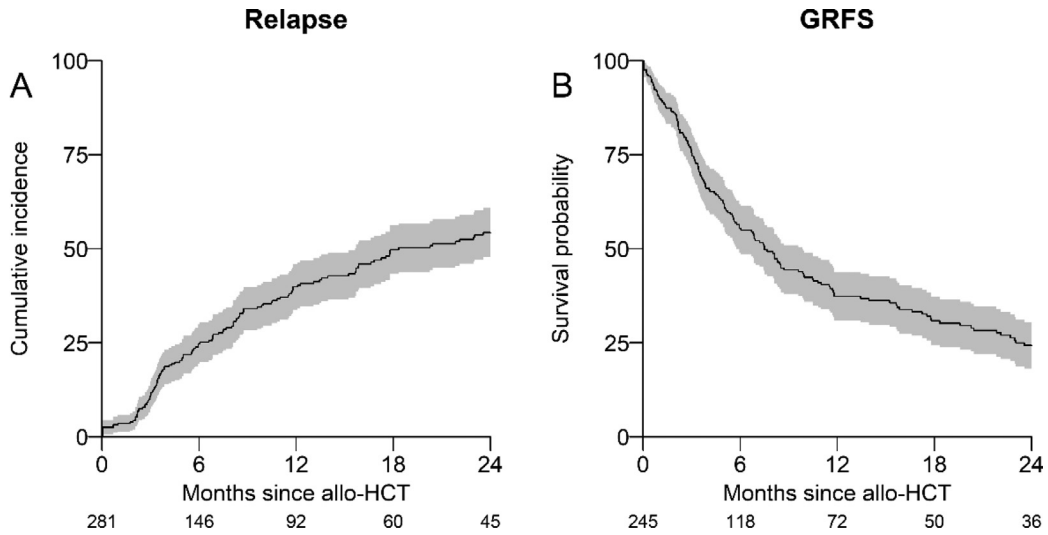

Figure 4. (A) Cumulative incidence of relapse. (B) GFRS.

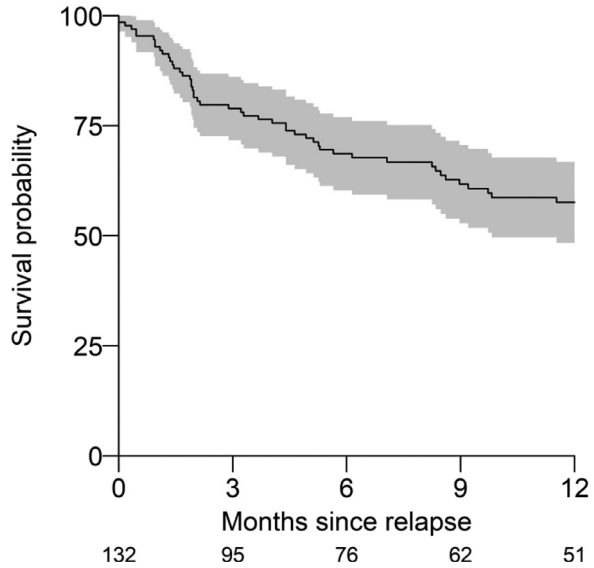

Figure 5. Post-relapse OS.

analysis. The cumulative incidence of platelet engraftment by day +100 was 84% (95% CI, 79% to 89%), with a median time to engraftment of 23 days (95% CI, 21 to 26 days). The median time to platelet engraftment was longer in the haplo group compared with the 3 non-haplo groups (27 days [95% CI, 25 to 33 days] versus 21 days [95% CI, 19 to 23 days]; $P < .001$). Day +100 platelet engraftment was significantly lower in the haplo group compared with the MRD, MUD, and MMRD/MMUD groups (74% [95% CI, 65% to 83%] versus 91% [95% CI, 83% to 98%], 92% [95% CI, 86% to 99%], and 82% [95% CI, 66% to 98%], respectively; $P < .001$).

The cumulative incidence of CR after HCT was 27% (95% CI, 21% to 32%) at day +100, 39% (95% CI, 33% to 46%) at 6 months, and 43% (95% CI, 37% to 50%) at 12 months. With respect to donor type, the cumulative incidence of CR at day +100 and 6 months was 19% (95% CI, 9% to 21%) and 37% (95% CI, 24% to 50%), respectively, for the MRD group; 25% (95% CI, 14% to 37%) and 39% (95% CI, 26% to 52%) for the MUD group; 34% (95% CI, 24% to 44%) and 51% (95% CI, 31% to 52%) for the haplo group, and 21% (95% CI, 3-39) and 40% (95% CI, 17-63) for the MMRD/MMUD group.

The cumulative incidence of acute GVHD by day +100 was 30% (95% CI, 25% to 36%) for grade II-IV and 9% (95% CI, 5% to 12%) for grade III-IV. The cumulative incidence of chronic GVHD by 2 years was 27% (95% CI, 21% to 32%), including 21% (95% CI, 17% to 28%) for limited chronic GVHD and 6% (95% CI, 3% to 9%) for extensive GVHD. There were no statistically significant differences by donor type (Figure 1).

With a median follow-up of 31.5 months (26.1 to 36.8 months), OS was 63% at 1 year (95% CI, 57% to 69%) and 51% at 2 years (95% CI, 45% to 58%) for the whole group, with no significant differences by donor type. PFS was 42% (95% CI, 36% to 49%) at 1 year and 26% (95% CI, 20% to 32%) at 2 years for all subjects, again without any significant differences among donor types (Figure 2). The cumulative incidence of NRM by 1 year was 18% (95% CI, 12% to 22%), and that by 2 years was 19% (95% CI, 14% to 24%) (Figure 3A-C). The rate of relapse was 54% at 2 years (95% CI, 45% to 61%) (Figure 4A). GRFS was 37% (95% CI, 31% to 44%) at 1 years and 24% (95% CI, 18% to 30%) at 2 years (Figure 4B). Furthermore, the OS rate postrelapse was 58% at 1 year (95% CI, 48% to 67%) (Figure 5). Causes of death are listed in Supplementary Table S1.

In univariate analysis, time from diagnosis, sex mismatch (female donor to male recipient), stem cell source, KPS score, era of transplantation (2012 to 2015 versus 2016 to 2018), and conditioning intensity were not predictive for OS, PFS, NRM, or relapse. Disease risk index (DRI) was predictive of OS ($P = .001$) and PFS ($P = .007$). Disease status $\geq$PR was significant for improved OS and PFS. Age was a significant factor for NRM, with a reduced NRM of 9% in patients age $<$50 years (Figure 3C). Because of missing data on the numbers of previous lines of therapy, we could not analyze the impact on outcomes. We also analyzed allo-HCT as second-line therapy or beyond versus upfront and found no impact on PFS, NRM, or relapse. We found an inferior impact on OS, but this result should be interpreted with caution because of the small number of patients analyzed (Supplementary Table S2). For acute GVHD, donor type, donor-recipient sex mismatch, age, time from diagnosis to HCT, conditioning intensity, and stem cell source were not significant; only the use of PT-Cy with a CNI with or without MMF was associated with a lower rate of acute GVHD. For chronic GVHD, no factor was significant. Use of a haplo donor compared with an MRD or MUD donor was

Table 3
Multivariable Analysis

Variable		OS		PFS		GRFS	
		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Donor							
	Haplo						
	MRD	0.6 (0.38-0.95)	.029	0.97 (0.65-1.44)	.9	0.89 (0.6-1.33)	.6
	MUD	0.68 (0.42-1.1)	.12	0.69 (0.46-1.04)	.08	0.63 (0.42-0.97)	.034
	MMRD + MMUD	1.08 (0.58-2.01)	.8	1.18 (0.7-2.01)	.5	0.93 (0.51-1.69)	.8
Age (decades)		1.2 (0.95-1.52)	.12	1.08 (0.88-1.31)	.5	1.08 (0.88-1.34)	.5
Disease stage at HCT							
	CR/VGPR						
	PR	1.25 (0.82-1.9)	.3	1.47 (1.03-2.12)	.036	1.42 (0.98-2.05)	.06
	<PR	1.86 (1.2-2.89)	.005	1.73 (1.16-2.56)	.007	1.4 (0.92-2.12)	.12
Time from diagnosis to HCT, yr		0.95 (0.89-1.02)	.18	1 (0.94-1.06)	.9	0.99 (0.93-1.05)	.7
MM classification							
	IgG						
	Other	1.64 (1.15-2.34)	.007	1.46 (1.07-2)	.018	1.26 (0.91-1.74)	.16
Donor-patient sex match							
	F->M						
	Other	0.72 (0.46-1.12)	.15	0.8 (0.54-1.19)	.3	0.8 (0.53-1.2)	.3
Conditioning intensity							
	MAC						
	Reduced	1.3 (0.88-1.93)	.19	1.42 (1.02-1.98)	.041	1.19 (0.84-1.67)	.3
KPS							
	<90						
	90-100	1.05 (0.72-1.53)	.8	0.91 (0.66-1.27)	.6	0.97 (0.7-1.35)	.9

associated with lower 2-year GRFS (Supplementary Tables S3 and S4). The median PFS and OS by donor type are displayed in Supplementary Table S5.

On multivariable analysis, disease status <PR before allo-HCT (HR, 1.86; 95% CI, 1.2 to 2.89; *P* = .005) and non-IgG subtype (HR, 1.64; 95% CI, 1.15 to 2.34; *P*=.007) were associated with inferior OS, and use of an MRD was associated with improved OS (HR, 0.6; 95% CI, 0.38 to 0.95; *P*= .029). For PFS, disease status PR (HR, 1.47; 95% CI, 1.03 to 2.12; *P*= .036) and <PR (HR, 1.73; 95% CI, 1.16 to 2.56; *P*= .007), and non-IgG subtype (HR 1.46; 95% CI, 1.07 to 2; *P*= .018) and RIC (HR, 1.42; 95% CI, 1.02 to 1.98; *P*= .041) were associated with inferior PFS. There was a trend toward improved PFS with use of an MUD (HR, 0.69; 95% CI, 0.46 to 1.04; *P*= .08). Use of an MUD was associated with improved GRFS (HR, 0.63; 95% CI, 0.42 to 0.97; *P* = .034). There was a trend toward inferior GRFS in patients in PR compared with those in CR/VGPR (HR, 1.42; 95% CI, 0.98 to 2.05; *P*= .06) (Table 3).

DISCUSSION

New immunotherapy-based strategies have provided impressive response rates in the range of 60% to 80% in patients with relapsed/refractory MM, but despite initial responses, many of these patients continue to relapse later [2,3,22]. To date, allo-HCT is the sole potentially curative therapy with long-term follow up available.

With advances in the prevention and treatment of acute and chronic GVHD, the outcomes from allo-HCT are expected to improve. Among new developments in the prevention of GVHD is the use of PT-CY as GVHD prophylaxis in combination with other agents, such as CNIs and MMF. The pioneering work of Luznik et al. [12] established the use of PTCy with other immunosuppressive medications in haplo-HCT, with a low incidence of acute and chronic GVHD and low NRM. We previously reported results of haploidentical allo-HCT in 96 patients with MM, 81% of whom received PTCy at EBMT/CIBMTR centers. We observed a cumulative incidence of 39% for acute GVHD grade II-IV by day +100 and of 46% for chronic GVHD by 2 years [23]. In a smaller study of 30 patients with MM who underwent haplo-HCT using PTCy, the researchers reported a cumulative incidence of 29% for acute GVHD grade II-IV by day +100 and of 7% for chronic GVHD by 18 months [24].

The use of PTCy has also been investigated in patients with hematologic malignancies who are undergoing allo-HCT using an MRD or MUD. Ruggeri et al. [18] reported the use of PTCy as GVHD prophylaxis in HLA-matched sibling or unrelated donor transplantation for patients with acute leukemia and found a rate of acute GVHD grade II-IV of 27.9% by day +100 and 33% by 1 year and a rate of extensive chronic GVHD of 18% when PTCy was used alone, 20% when PTCy was used with 1 immunosuppressive medication, and 9% when PTCy was combined with 2 immunosuppressive medications. Data on 40 patients with MM presented in an abstract form reported results using PTCy as GVHD prophylaxis with thiotepa and busulfan conditioning reported a cumulative incidence of acute GVHD of 26% at day +100 and of chronic GVHD of 48% at 2 years [25]. In another study, the use of CD34 cell selection as a method of GVHD prophylaxis was associated with low incidences of acute GVHD grade II-IV (7% at day +100 and 18% at day +180) and chronic GVHD (8% at 1 year and 11% at 2 years) [26]. Post-transplantation DLI was administered to 40% of the patients. The incidence of relapse was 47% at 3 years. These results are encouraging; however, this technology is not yet widely available.

In our analysis of the largest MM cohort using PTCy among different donor types, we observed cumulative incidences of acute GVHD grade II-IV (30%) and grade III-IV (9%) and chronic GVHD (27%; 6% for extensive chronic GVHD) that compare favorably with historical results for allo-HCT using standard GVHD

prophylaxis that show an incidence of acute GVHD grade II-IV in the range of 40%-50%, of grade III-IV of 11%, of chronic GVHD in the range of 40%-55%, and of extensive chronic GVHD of 24%-30% [5,7,27,28]. Importantly, there was no obvious difference based on donor type.

Neutrophil engraftment occurred at a median of 19 days, with no difference among donor types, which may be longer than that reported with standard immunosuppressive therapy. Platelet engraftment was delayed with haplo allo-HCT compared with allo-HCT using the other donor types. A similar observation has been reported with delayed platelet engraftment with haplo-HCT [21,29,30].

In this study, we observed an encouraging OS, given that the fact that these patients were multiply relapsed, many of whom had undergone 2 auto-HCTs before allo-HCT. Indeed, despite the relapse rate of 54% at 2 years, the postrelapse OS was 58% (95% CI, 48% to 67%) at 1 year, providing an allogeneic transplantation platform for new immune-therapeutic agents. Disease status <PR was predictive of lower PFS and OS, as expected. With the availability of new immune-based strategies with impressive disease control rates, these new options may serve as a bridge to allo-HCT in appropriate younger patients in whom NRM is expected to be low. This strategy has been explored successfully in patients with acute lymphoblastic leukemia [31]. In addition, we found a GRFS rate of 24% at 2 years, emphasizing the need for investigating new therapeutic interventions for further control of both disease and GVHD. Interestingly, use of an MUD was associated with improved GRFS on multivariate analysis. We also observed improved OS with MRD HCT compared with haplo-HCT on multivariable analysis. In summary, our results support the selection of MRDs and MUDs over haplo donors in the context of PTCy in allo-HCT for MM.

Limitations of our study include the retrospective nature of our analysis, missing data on previous lines of therapy, and the absence of information on cytogenetic/fluorescence in situ hybridization abnormalities at the time of allo-HCT. Furthermore, the small number of MMRD/MMUDs limits our ability to draw definitive conclusions for this subgroup.

In conclusion, the use of PTCy in MM patients undergoing allo-HCT using different donor types was associated with low incidences of acute and chronic GVHD. This approach led to favorable OS in the MRD setting and improved GRFS when using MUDs. NRM was particularly low in younger patients. Future trials of allo-HCT in MM patients may benefit from incorporating PTCy as immunosuppression, and this might be especially beneficial in the matched donor setting.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2021.09.008.

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