

Late outcomes after posttransplant cyclophosphamide-based GVHD prophylaxis in patients with AML: an ALWP-EBMT study

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Key Points

- HLA matching did not affect late transplantation outcomes after PT-Cy-based GVHD prophylaxis.
- Older donor age and female-to-male donor-recipient sex mismatch were associated with increased late NRM.

Data on late events after allogeneic hematopoietic stem cell transplantation (allo-HSCT) with posttransplant cyclophosphamide (PT-Cy)-based graft-versus-host disease (GVHD) prophylaxis in patients with acute myeloid leukemia (AML) remain very limited. We analyzed long-term outcomes in 1289 patients from the European Society for Blood and Marrow Transplantation registry who underwent PT-Cy-based allo-HSCT for AML in first remission from haploidentical (n = 906), 10/10 matched unrelated donors (MUD, n = 208), or matched sibling donors (MSD, n = 175), and who remained leukemia-free 2 years after transplantation. At 2 years from the landmark, the cumulative incidence of relapse and nonrelapse mortality (NRM) was 6% and 4% in haploidentical, 7% and 3% in MUD, and 8% and 4% in MSD recipients, respectively. Similarly, 2-year estimates of leukemia-free survival and overall survival were 91% and 93% for haploidentical, 90% and 95% for MUD, and 88% and 93% for MSD recipients, respectively. No statistically significant association was found between donor type and long-term transplantation outcomes. In contrast, transplantation from a female donor to a male recipient (hazard ratio [HR], 2.70; *P* = .013) and older donor age (HR per 10-year increase, 1.34; *P* = .036) were associated with increased risk of late NRM. These associations were confirmed in subanalyses in the haploidentical cohort. Notably, no factors associated with late relapse were identified in the multivariable models. PT-Cy-based allo-HSCT is associated with favorable outcomes in patients with AML who remain leukemia-free 2 years after transplant. Long-term outcomes after haploidentical allo-HSCT were comparable with those of 10/10 MUD or MSD recipients in the setting of PT-Cy GVHD prophylaxis.

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Data are available from the corresponding author, Eduardo Rodríguez-Arboli (eduardo.rodriguez.arboli.sspa@juntadeandalucia.es), on request.

The full-text version of this article contains a data supplement.

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Introduction

The introduction of posttransplant cyclophosphamide (PT-Cy)-based graft-versus-host disease (GVHD) prophylaxis has revolutionized haploidentical allogeneic hematopoietic stem cell transplantation (allo-HSCT), effectively mitigating HLA barriers. This strategy has markedly reduced the risk of GVHD, which historically limited the use of haploidentical donors.¹⁻³ Compelling results in the haploidentical allo-HSCT setting have led to the increasing adoption of PT-Cy across other donor types, with emerging data indicating favorable outcomes after transplantation from HLA-matched sibling donors (MSD) and HLA-matched unrelated donors (MUD).⁴⁻¹¹ Previous studies aiming to compare donor types were limited by difficulties in isolating the impact of HLA matching from other differential factors in the transplantation platforms typically associated with each donor category. In this regard, the homogenization of GVHD prophylaxis through the use of PT-Cy has enabled more direct analyses of donor type-specific effects. Data from these analyses suggest that, when using PT-Cy-based platforms, outcome differences between haploidentical donors, MUD, and MSD are largely attenuated.¹²⁻¹⁴

Multiple studies have reported results after PT-Cy-based allo-HSCT in patients with acute myeloid leukemia (AML).^{12,15,16} However, data on long-term outcomes and late posttransplant events remain very limited.¹⁷ Although most leukemia relapses and transplant-related complications occur within the first 2 years after allo-HSCT, late events continue to contribute substantially to excess morbidity and mortality among long-term survivors.¹⁸⁻²³ Additionally, different transplantation platforms can be associated with distinct relapse mechanisms and dynamics, as well as unique toxicity profiles, which may also influence the incidence patterns and nature of late events.²⁴⁻²⁹ Therefore, there is a need to specifically assess long-term outcomes in the context of PT-Cy-based platforms.

In this report, we analyzed long-term outcomes and predictors of late events in a large cohort of patients included in the European Society for Blood and Marrow Transplantation (EBMT) registry who underwent allo-HSCT with PT-Cy-based GVHD prophylaxis from a haploidentical donor, MUD, or MSD, and who remained leukemia-free 2 years after transplantation.

Methods

Data collection

This study was a retrospective, multicenter, registry-based analysis conducted on behalf of the Acute Leukemia Working Party (ALWP) of the EBMT. The EBMT is a nonprofit scientific organization representing >600 transplantation centers. EBMT collaborating centers are required to report all consecutive allo-HSCTs and provide annual follow-up data. Regular in-house and external data audits are carried out to ensure data accuracy. In compliance with the 1975 Helsinki Declaration, all centers must obtain written informed consent from patients for the use of their personal information for research purposes before registering their data in the EBMT registry. The study was approved by the institutional review boards of all participating institutions.

Study population

Eligibility criteria were age ≥ 18 years; AML in first complete remission; first allo-HSCT from a haploidentical donor, 10/10 MUD,

or MSD performed between 2010 and 2022; peripheral blood or bone marrow graft; and PT-Cy-containing GVHD prophylaxis. The analyses were restricted to patients who remained leukemia-free at 2 years after allo-HSCT. Patients who received ex vivo T-cell-depleted allografts were excluded.

End points and definitions

Study end points included overall survival (OS), leukemia-free survival (LFS), cumulative incidence of relapse (CIR), nonrelapse mortality (NRM), chronic GVHD (cGVHD), cGVHD relapse-free survival (cGRFS), and cause of death. All time-to-event end points were analyzed from a landmark at 2 years after allo-HSCT. OS was defined as the time to death due to any cause. LFS was defined as the time to first documentation of leukemia relapse (ie, detection of bone marrow blasts of $\geq 5\%$, reappearance of blasts in the peripheral blood, or development of extramedullary disease) or death. CIR was defined as the time to first documentation of leukemia relapse. NRM was defined as the time to death from any cause without previous documentation of leukemia relapse. cGRFS was defined as survival free of events, including extensive cGVHD, leukemia relapse, or death. Patients with no event were censored at the date of their last follow-up.

Statistical analysis

Patient, disease, and transplantation characteristics were compared across donor types using the Kruskal-Wallis rank-sum test for continuous variables and the Pearson χ^2 test for categorical variables. Probabilities of LFS, OS, and cGRFS were estimated using the Kaplan-Meier method. Cumulative incidence functions were used to estimate the probabilities of CIR, NRM, and cGVHD in the setting of competing risks. Competing events were death for CIR, relapse for NRM, and relapse or death for cGVHD. The follow-up time was calculated using the reverse Kaplan-Meier method. Univariate analyses were performed using the log-rank test for LFS, OS, and cGRFS, and Gray's test for CIR, NRM, and cGVHD. Cox regression was used to assess the association between covariates of interest and LFS and OS. Cause-specific regression models were used for relapse and NRM, accounting for competing risks. To take center effects into account, a random effect or frailty for each center was introduced into the models. Two-sided *P* values are reported. Statistical analyses were conducted in R version 4.1.1 (R Development Core Team, URL: <https://www.R-project.org/>).

Results

Cohort characteristics

Patient, disease, and transplantation characteristics are shown in Table 1. During the study period, 3933 patients with AML in first complete remission underwent a PT-Cy-based allo-HSCT (2598 from haploidentical donors, 765 from MUDs, and 570 from MSDs). A total of 1289 patients with a median age of 53 years (range, 18-75) remained leukemia-free 2 years after transplantation and were included in the analyses. Of these, 906 (70%) underwent allo-HSCT from haploidentical donors, 208 (16%) from 10/10 MUDs, and 175 (14%) from MSDs. Patient cohorts, categorized by donor group, differed across multiple characteristics. Briefly, median age at the time of transplantation was higher among haploidentical and MUD recipients (haploidentical,

Table 1. Patient, disease, and transplant characteristics

Variable	All patients (N = 1289)	Donor type			P value
		Haploidentical (n = 906)	MUD (n = 208)	MSD (n = 175)	
Median follow-up from landmark, y (95% CI)	2.0 (1.9-2.1)	2.0 (1.8-2.1)	2.2 (2.0-2.6)	2.0 (1.5-2.4)	
Patient age at the time of allo-HSCT, y					.028
Median (IQR)	53 (41-62)	53 (41-61)	55 (42-64)	50 (40-59)	
Range	18-75	18-75	18-73	18-71	
Patient female sex, n (%)	553 (43)	386 (43)	88 (42)	79 (45)	.81
Karnofsky performance score, n (%)					<.001
≥90	993 (80)	721 (83)	148 (72)	124 (73)	
<90	254 (20)	150 (17)	58 (28)	46 (27)	
Missing	42	35	2	5	
HCT-CI score, n (%)					.076
0	598 (57)	430 (58)	84 (50)	84 (61)	
1-2	229 (22)	149 (20)	47 (28)	33 (24)	
≥3	217 (21)	160 (22)	36 (22)	21 (15)	
Missing	245	167	41	37	
Cytogenetic risk, n (%)					.87
Favorable	50 (5)	36 (5)	7 (4)	7 (5)	
Intermediate	777 (75)	548 (74)	127 (77)	102 (77)	
Adverse	211 (20)	156 (21)	32 (19)	23 (17)	
Missing	251	166	42	43	
Time between diagnosis and allo-HSCT, mo					<.001
Median (IQR)	4.9 (3.8-6.5)	5.1 (4.0-6.7)	4.6 (3.6-6.2)	4.4 (3.4-5.5)	
Range	1.1-18.0	1.3-17.9	1.8-18.0	1.1-17.6	
Stem cell source, n (%)					<.001
Peripheral blood	935 (73)	585 (65)	194 (93)	156 (89)	
Bone marrow	354 (27)	321 (35)	14 (7)	19 (11)	
Donor age, y					<.001
Median (IQR)	36 (27-47)	36 (27-46)	28 (23-34)	51 (39-59)	
Range	11-71	11-71	18-59	13-71	
Missing	83	25	31	27	
Female donor to male recipient, n (%)					.46
Yes	237 (18)	171 (19)	32 (15)	34 (20)	
Missing	1	0	0	1	
Donor/patient CMV serostatus, n (%)					<.001
Negative/negative	223 (18)	141 (16)	49 (24)	33 (19)	
Negative/positive	247 (20)	169 (19)	56 (27)	22 (13)	
Positive/negative	96 (8)	64 (7)	17 (8)	15 (9)	
Positive/positive	698 (55)	512 (58)	85 (41)	101 (59)	
Missing	25	20	1	4	
Conditioning intensity, n (%)					<.001
RIC	432 (34)	299 (33)	83 (40)	50 (29)	
MAC-TBI	86 (7)	45 (5)	24 (12)	17 (10)	
MAC-Chemotherapy	767 (60)	560 (62)	101 (49)	106 (61)	
Missing	4	2	0	2	

Bold face values indicate $P < .05$. Variable names are bold.

ATG, antithymocyte globulin; Bu, busulfan; CMV, cytomegalovirus; Flu, fludarabine; IQR, interquartile range; MAC, myeloablative conditioning; Mel, melphalan; MMF, mycophenolate mofetil; MTX, methotrexate; RIC, reduced-intensity conditioning; Tacro, tacrolimus; TBF, thiotepa-busulfan-fludarabine; TBI, total body irradiation; TCI, transplant conditioning intensity; Treo, treosulfan.

Table 1 (continued)

Variable	All patients (N = 1289)	Donor type			P value
		Haploidentical (n = 906)	MUD (n = 208)	MSD (n = 175)	
TCI score, n (%)					<.001
1-2	349 (29)	233 (28)	72 (39)	44 (27)	
2.5-3.5	646 (54)	510 (60)	69 (37)	67 (41)	
4-6	202 (17)	104 (12)	45 (24)	53 (32)	
Missing	92	59	22	11	
Conditioning regimen, n (%)					
TBI-based	234 (18)	137 (15)	61 (29)	36 (21)	
TBF-based	545 (42)	504 (56)	15 (7)	26 (15)	
Treo/Flu-based	102 (8)	62 (7)	23 (11)	17 (10)	
Flu/Bu-based	299 (23)	148 (16)	81 (39)	70 (40)	
Bu/Cy-based	45 (4)	8 (1)	21 (10)	16 (9)	
Flu/Mel-based	45 (4)	34 (4)	4 (2)	7 (4)	
Other	19 (2)	13 (1)	3 (1)	3 (2)	
Main GVHD prophylaxis, n (%)					<.001
PT-Cy	1142 (89)	826 (91)	165 (79)	151 (86)	
PT-Cy + ATG	147 (11)	80 (9)	43 (21)	24 (14)	
Associated GVHD prophylaxis					
CsA	110 (9)	19 (2)	43 (21)	48 (27)	
MTX	1 (<0.1)	0 (0)	1 (1)	0 (0)	
MMF	26 (2)	16 (2)	5 (2)	5 (3)	
MMF + CsA	620 (48)	555 (61)	41 (20)	24 (14)	
MMF + CsA + Tacro	14 (1)	12 (1)	1 (1)	1 (1)	
MMF + sirolimus	61 (5)	31 (3)	24 (12)	6 (3)	
MMF+ Tacro	253 (20)	224 (25)	17 (8)	12 (7)	
MTX + CsA	21 (2)	7 (1)	8 (4)	6 (3)	
MTX + MMF	1 (<0.1)	0 (0)	1 (1)	0 (0)	
MTX + Tacro	4 (0.3)	1 (0.1)	1 (1)	2 (1)	
Tacro	85 (7)	24 (3)	39 (19)	22 (13)	
Other	93 (7)	17 (2)	27 (13)	49 (28)	

Bold face values indicate $P < .05$. Variable names are bold.

ATG, antithymocyte globulin; Bu, busulfan; CMV, cytomegalovirus; Flu, fludarabine; IQR, interquartile range; MAC, myeloablative conditioning; Mel, melphalan; MMF, mycophenolate mofetil; MTX, methotrexate; RIC, reduced-intensity conditioning; Tacro, tacrolimus; TBF, thiotepa-busulfan-fludarabine; TBI, total body irradiation; TCI, transplant conditioning intensity; Treo, treosulfan.

53 years; MUD, 55 years; MSD, 50 years; $P = .028$), and a lower proportion of patients in the haploidentical group had a Karnofsky performance score of <90 (haploidentical, 17%; MUD, 28%; MSD, 27%; $P < .001$). Cytogenetic risk and hematopoietic cell transplantation comorbidity index [HCT-CI] scores were balanced across cohorts. Regarding the transplantation platform, bone marrow grafts were more frequently used in the haploidentical group (haploidentical, 35%; MUD, 7%; MSD, 11%; $P < .001$). Median donor age was substantially higher in the MSD group (haploidentical, 36 years; MUD, 28 years; MSD, 51 years; $P < .001$). Additionally, a higher proportion of patients in the MUD group received a reduced-intensity conditioning regimen (haploidentical, 33%; MUD, 40%; MSD, 29%; $P < .001$). The most commonly used conditioning regimens were thiotepa-busulfan-fludarabine in the haploidentical group (56%) and fludarabine-busulfan in both the MUD (39%) and MSD (40%) groups. Similarly, GVHD prophylaxis strategies associated with PT-Cy

varied significantly across and within groups. In the haploidentical group, mycophenolate mofetil (MMF) and cyclosporine (CsA) were the most commonly used combination (61%), whereas in the MUD group, CsA (21%), MMF/CsA (20%), and tacrolimus (19%) were used with comparable frequency. In the MSD group, CsA was the most common choice (27%), followed by MMF/CsA (14%) and tacrolimus (13%). Overall, 11% of patients received antithymocyte globulin in addition to PT-Cy, with this combination being more frequently used in the MUD and MSD groups (haploidentical, 9%; MUD, 21%; MSD, 14%; $P < .001$).

Long-term transplantation outcomes

Two-year outcomes from the time of allo-HSCT (N = 3933) are shown in supplemental Table 1. In summary, 2-year OS was 67% (95% confidence interval [CI], 65-68), and 2-year LFS was 60% (95% CI, 59-62), with similar results across donor types. Two-year NRM was higher in the haploidentical group (20% [95% CI,

18-22]) compared with the MUD (10% [95% CI, 8-13]) and MSD (11% [95% CI, 8-14]) groups. This was compensated by a lower CIR in the haploidentical group (21% [95% CI, 19-23] vs 26% [95% CI, 22-29] for MUDs and 29% [95% CI, 25-33] for MSDs). The incidence of grade 2 to 4 acute GVHD was lowest in the MSD group (19% [95% CI, 16-22]) followed by the MUD (23% [95% CI, 20-26]) and haploidentical (26% [95% CI, 24-28]) groups. Rates of cGVHD were similar among groups (haploidentical, 30% [95% CI, 29-32]; MUD, 29% [95% CI, 25-33]; and MSD, 34% [95% CI, 30-39]), as were rates of extensive cGVHD (haploidentical, 11% [95% CI, 10-12]; MUD, 12% [95% CI, 10-15]; and MSD, 16% [95% CI, 13-20]). Multivariate models for 2-year outcomes in this cohort are shown in supplemental Table 2. Results from analyses of a subset of this cohort have been published previously.¹²

Transplantation outcomes from the 2-year landmark are summarized in Table 2. Median follow-up after the landmark was 2 years (95% CI, 1.9-2.1). The 2- and 5-year estimates of CIR in the haploidentical cohort were 6% (95% CI, 4-8) and 9% (95% CI, 7-12), respectively; the 2- and 5-year estimates of NRM were 4% (95% CI, 2-5) and 9% (95% CI, 6-13), respectively. Likewise, the 2- and 5-year estimates of LFS in the haploidentical group were 91% (95% CI, 88-93) and 82% (95% CI, 77-86), respectively, and the OS estimates were 93% (95% CI, 91-95) and 85% (95% CI, 80-89), respectively. In the MUD cohort, 2-year estimates of CIR, NRM, LFS, and OS were 7% (95% CI, 4-12), 3% (95% CI, 1-7), 90% (95% CI, 84-94), and 95% (95% CI, 91-98), respectively, whereas the corresponding 5-year estimates were 14% (95% CI, 8-21), 3% (95% CI, 1-7), 83% (95% CI, 75-89), and 78% (95% CI, 65-87), respectively. Lastly, in the MSD cohort, the corresponding 2-year estimates were 8% (95% CI, 4-13), 4% (95% CI, 2-8), 88% (95% CI, 82-93), and 93% (95% CI, 86-96), and the 5-year estimates were 12% (95% CI, 7-20), 4% (95% CI, 2-8), 84% (95% CI, 75-90), and 91% (95% CI, 83-95), respectively (Table 2; Figure 1).

Among those patients who remained cGVHD-free at the landmark (n = 518 [57%] for haploidentical, n = 121 [57%] for MUD, and n = 95 [54%] for MSD), the 2-year cumulative incidence of cGVHD was 4% (95% CI, 2-6), 1% (95% CI, 0.1-5), and 6% (95% CI, 2-14), in the haploidentical, MUD, and MSD groups, respectively. Corresponding 5-year estimates were 7% (95% CI, 4-11), 1% (95% CI, 0.1-5), and 13% (95% CI, 5-26), respectively (Table 2; Figure 2). Similarly, the 2-year cumulative incidence of

extensive cGVHD was 1% (95% CI, 1-3) and 5% (95% CI, 1-16) in the haploidentical and MSD groups, respectively. Corresponding 5-year estimates were 2% (95% CI, 1-5) and 5% (95% CI, 1-16). There were no late extensive cGVHD events reported in the MUD group (Table 2). A total of 157 patients (17%) in the haploidentical group, 49 (24%) in the MUD group, and 42 (24%) in the MSD group had a previous history of extensive cGVHD before the landmark and were therefore excluded from the cGRFS analysis. The 2- and 5-year estimates of cGRFS were 92% (95% CI, 88-95) and 87% (95% CI, 78-93) in the haploidentical group, 91% (95% CI, 79-96) and 91% (95% CI, 79-96) in the MUD group, and 90% (95% CI, 75-96) and 83% (95% CI, 60-93) in the MSD group, respectively (Table 2; Figure 2).

Causes of late mortality

There were 60 deaths in the haploidentical group, 17 in the MUD group, and 12 in the MSD group. The most common cause of death across all 3 cohorts was leukemia related (haploidentical, n = 27 [45%]; MUD, n = 12 [71%]; MSD, n = 6 [50%]). Secondary malignancies resulting in death were reported in 7 (12%) patients in the haploidentical group and 2 (12%) patients in the MUD group. GVHD accounted for 4 (7%) deaths in the haploidentical group and 1 (8%) death in the MSD group. Infection-related deaths occurred in 8 patients (13%) in the haploidentical group, 1 (6%) in the MUD group, and 2 (17%) in the MSD group. Additionally, infections in the setting of GVHD contributed to 2 deaths (3%) in the haploidentical group, 1 (6%) in the MUD group, and 2 (17%) in the MSD group. Cause of death is detailed in Table 3.

Multivariate analyses of long-term transplantation outcomes

Multivariate models of long-term transplantation outcomes were constructed for the full patient cohort (Table 4) and separately for the haploidentical cohort (supplemental Table 3). The more limited sample sizes in the MUD and MSD cohorts precluded reliable model fitting in these subgroups.

In the full cohort analysis, no statistically significant association was found between donor type and long-term transplantation outcomes, although a nonsignificant trend toward higher NRM was noted for haploidentical donors than for MSDs (hazard ratio [HR], 4.30; 95% CI, 0.86-21.50; P = .08; Table 4). In contrast, donor characteristics other than donor HLA matching were predictive of

Table 2. Transplantation outcomes from the 2-year landmark, stratified by donor type

	Outcome by donor type, % (95% CI)					
	Haploidentical		MUD		MSD	
	2 y	5 y	2 y	5 y	2 y	5 y
NRM	4 (2-5)	9 (6-13)	3 (1-7)	3 (1-7)	4 (2-8)	4 (2-8)
CIR	6 (4-8)	9 (7-12)	7 (4-12)	14 (8-21)	8 (4-13)	12 (7-20)
LFS	91 (88-93)	82 (77-86)	90 (84-94)	83 (75-89)	88 (82-93)	84 (75-90)
OS	93 (91-95)	85 (80-89)	95 (91-98)	78 (65-87)	93 (86-96)	91 (83-95)
cGRFS	92 (88-95)	87 (78-93)	91 (79-96)	91 (79-96)	90 (75-96)	83 (60-93)
cGVHD	4 (2-6)	7 (4-11)	1 (0.1-5)	1 (0.1-5)	6 (2-14)	13 (5-26)
Extensive cGVHD	1 (1-3)	2 (1-5)	0	0	5 (1-16)	5 (1-16)

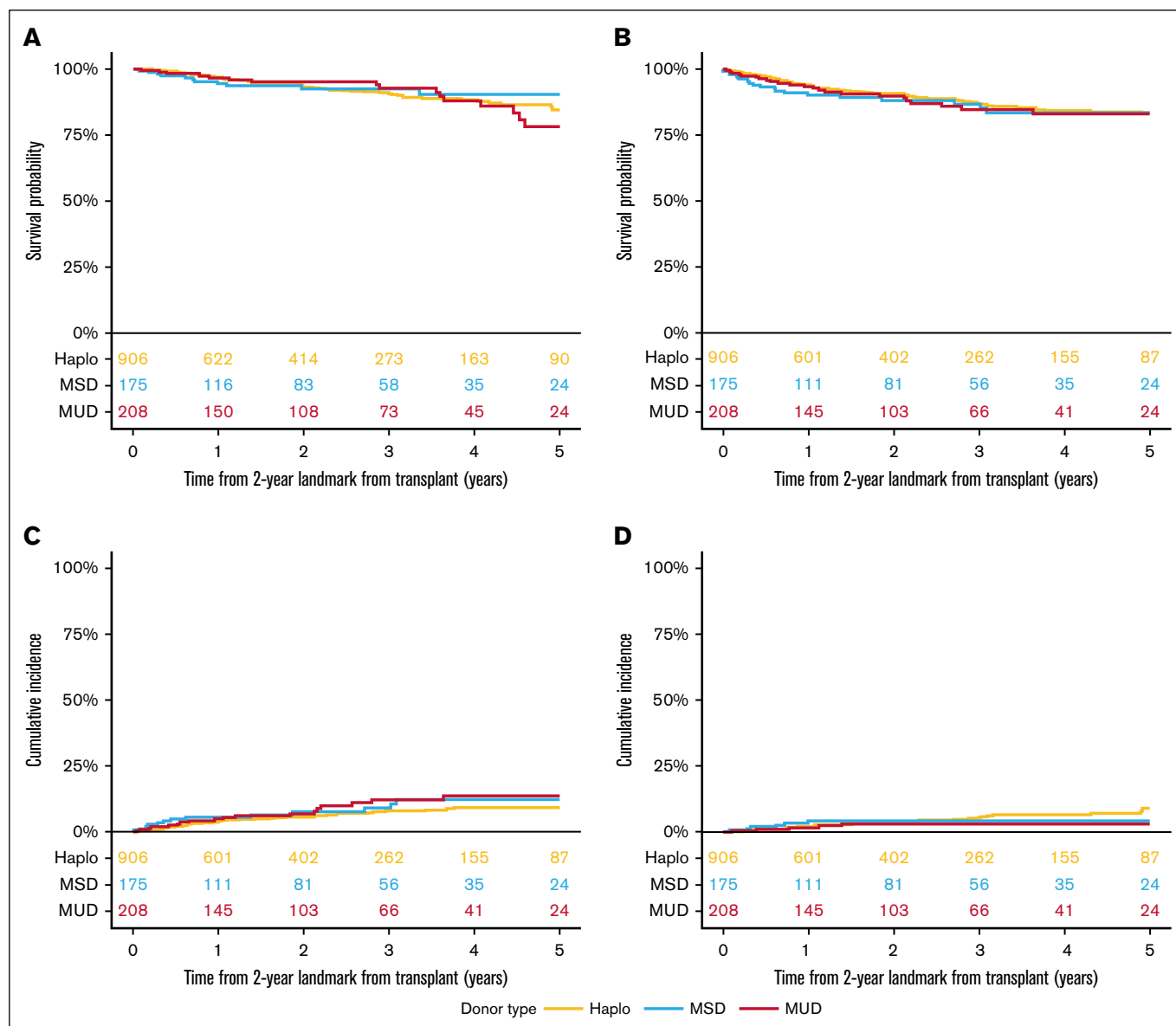


Figure 1. Long-term outcomes from 2 years after transplantation, stratified by donor type. (A) OS, (B) LFS, (C) CIR, and (D) NRM. Haplo, haploidentical.

late NRM. Specifically, transplantation from a female donor to a male recipient was associated with increased NRM (HR, 2.70; 95% CI, 1.23-5.94; $P = .013$), resulting in decreased LFS (HR, 1.82; 95% CI, 1.11-2.99; $P = .018$), and OS (HR, 2.10; 95% CI, 1.16-3.80; $P = .014$). Similarly, older donor age was associated with increased NRM (HR per 10-year increase, 1.34 [95% CI, 1.00-1.97]; $P = .036$), although no statistically significant detrimental impact on OS was observed (HR per 10-year increase, 1.22 [95% CI, 1.00-1.48]; $P = .10$). Additionally, older patient age showed a nonstatistically significant trend toward increased NRM risk (HR per 10-year increase, 1.41 [95% CI, 1.00-2.01]; $P = .05$) and decreased OS (HR per 10-year increase, 1.28 [95% CI, 1.01-1.63]; $P = .043$). No other patient-related (Karnofsky performance score, HCT-CI score, donor/recipient cytomegalovirus serostatus), disease-related (cytogenetic risk), or transplant-related factor (conditioning intensity) included in the final models was identified

as being independently associated with long-term transplantation outcomes. Most notably, the multivariable models did not reveal any factors associated with late relapse.

Separate models were constructed in the haploidentical cohort. These analyses confirmed the previously described associations between older donor age and increased risk of NRM (HR per 10-year increase, 1.48 [95% CI, 1.00-2.16]; $P = .026$), as well as between transplantation from a female donor to a male recipient and higher NRM risk (HR, 3.03; 95% CI, 1.20-7.60; $P = .018$). Additionally, a history of cGVHD before the 2-year landmark (HR, 2.77; 95% CI, 1.13-6.81; $P = .026$), and an HCT-CI score of ≥ 3 (compared with HCT-CI score of 0; HR, 2.90; 95% CI, 1.08-7.78; $P = .034$) were also associated with increased risk of late NRM. As observed in the full cohort, no predictors of late relapse were identified.

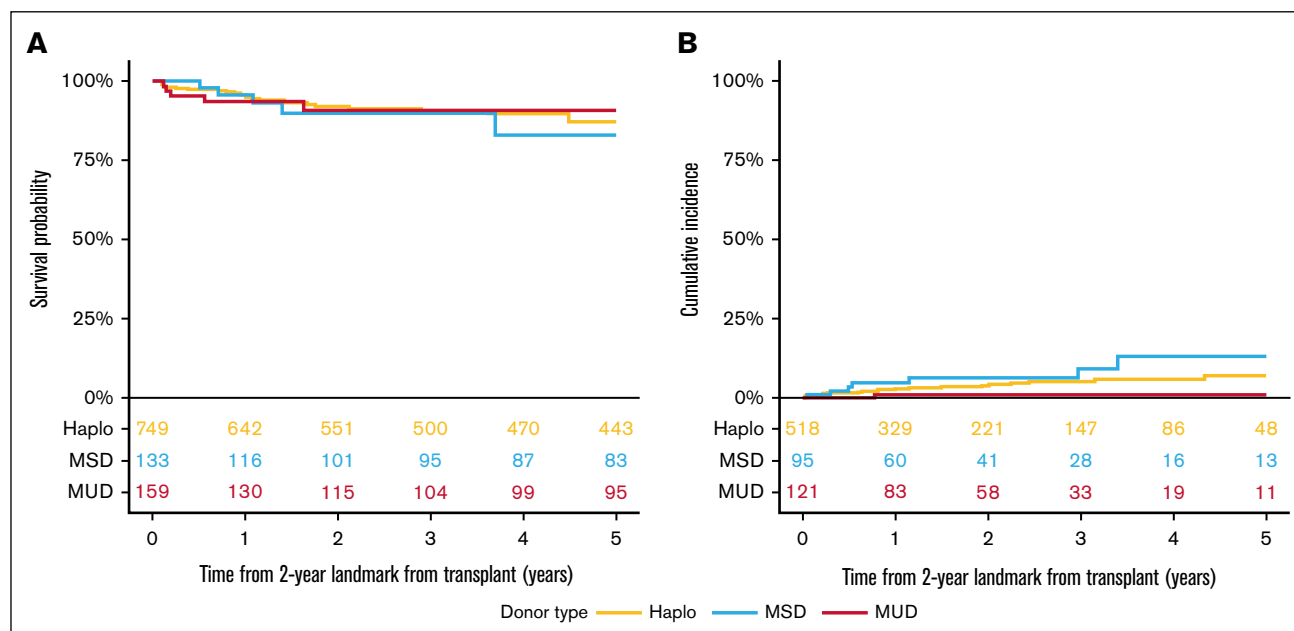


Figure 2. Long-term outcomes from 2 years after transplantation, stratified by donor type. (A) cGRFS, (B) cumulative incidence of cGVHD.

Discussion

Although PT-Cy is increasingly adopted as the preferred GVHD prophylaxis strategy across different donor types, current evidence is largely derived from studies with limited follow-up. To our knowledge, this is the first report to evaluate long-term outcomes of PT-Cy-based allo-HSCT platforms in a population of patients with AML. With cGRFS, OS, and LFS estimates of 87%, 84%, and 82% at 5 years from the landmark, respectively, our analyses confirm favorable long-term outcomes in patients with AML who remain leukemia-free 2 years after transplant. Reassuringly, our results are consistent with those of a recent ALWP-EBMT platform-agnostic analysis.²³ In that study, reported outcomes at 5 and 10 years from transplantation were 80% and 68% for cGRFS, 88% and 76% for OS, and 84% and 72% for LFS, respectively. Of note, 95% of patients in that cohort underwent transplantation from MSD or MUD, and only 1.5% received PT-Cy prophylaxis. Thus, acknowledging the limitations of cross-study comparisons, our data indicate no major differences in outcomes beyond 2 years

between PT-Cy-based and other conventional allo-HSCT platforms.

A major finding of our study is that the degree of HLA matching does not appear to affect late transplantation outcomes in the setting of PT-Cy-based GVHD prophylaxis. Donor type was not associated with long-term CIR, LFS, or OS, although there was a nonstatistically significant trend toward higher late NRM after haploidentical transplantation. Previous shorter-term analyses from the EBMT registry reported higher rates of grade 3/4 acute GVHD and NRM, but a lower risk of relapse, resulting in no differences in LFS or OS among patients with AML after haploidentical compared with MUD or MSD transplantation in the setting of PT-Cy prophylaxis.¹² Thus, our results further support the notion that the importance of HLA matching is attenuated when homogeneous PT-Cy GVHD prophylaxis is used, and that additional factors, such as expected delays to transplantation and specific donor characteristics other than HLA compatibility, should be given greater consideration when selecting between a MUD and a haploidentical donor.^{12,13,15}

Table 3. Cause of death

Cause of death	All patients (N = 89), n (%)	Donor type		
		Haploidentical (n = 60), n (%)	MUD (n = 17), n (%)	MSD (n = 12), n (%)
Leukemia	45 (51)	27 (45)	12 (71)	6 (50)
Infection	11 (12)	8 (13)	1 (6)	2 (17)
Secondary malignancy	9 (10)	7 (12)	2 (12)	0
GVHD	5 (6)	4 (7)	0	1 (8)
GVHD + infection	5 (6)	2 (3)	1 (6)	2 (17)
Organ toxicity	3 (3)	2 (3)	1 (6)	0
Other (transplant-related)	1 (1)	1 (2)	0	0
Other	10 (11)	9 (15)	0	1 (8)

Table 4. Multivariable analysis of transplantation outcomes

Variable	NRM		CIR		LFS		OS	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Donor type								
MSD	Reference		Reference		Reference		Reference	
10/10 MUD	3.82 (0.60-24.37)	.16	1.36 (0.48-3.8)	.56	1.74 (0.71-4.27)	.22	1.86 (0.59-5.87)	.29
Haploidentical donor	4.30 (0.86-21.50)	.08	0.76 (0.33-1.74)	.51	1.28 (0.61-2.65)	.51	1.73 (0.67-4.48)	.26
Karnofsky performance score								
<90	Reference		Reference		Reference		Reference	
≥90	0.77 (0.33-1.82)	.56	0.79 (0.41-1.51)	.48	0.77 (0.46-1.29)	.33	0.80 (0.42-1.49)	.48
Age (per 10-year increase)	1.41 (1.00-2.01)	.05	1.08 (0.86-1.35)	.51	1.17 (0.97-1.41)	.10	1.28 (1.01-1.63)	.043
Donor age (per 10-year increase)	1.34 (1.00-1.97)	.036	1.10 (0.82-1.34)	.48	1.22 (1.00-1.34)	.10	1.22 (1.00-1.48)	.10
Female donor to male recipient								
No	Reference		Reference		Reference		Reference	
Yes	2.70 (1.23-5.94)	.013	1.47 (0.76-2.83)	.25	1.82 (1.11-2.99)	.018	2.10 (1.16-3.80)	.014
Conditioning intensity								
RIC	Reference		Reference		Reference		Reference	
MAC	1.10 (0.45-2.65)	.84	2.04 (0.98-4.21)	.06	1.57 (0.92-2.67)	.10	1.39 (0.73-2.64)	.31
Cytogenetic risk								
Favorable/intermediate/missing	Reference		Reference		Reference		Reference	
Adverse	1.10 (0.44-2.77)	.84	1.54 (0.80-2.95)	.20	1.36 (0.8-2.31)	.25	1.61 (0.87-2.98)	.13
HCT-CI score								
0	Reference		Reference		Reference		Reference	
1-2	1.43 (0.55-3.76)	.46	0.44 (0.18-1.06)	.07	0.69 (0.37-1.29)	.24	1.08 (0.54-2.16)	.84
≥3	1.95 (0.82-4.62)	.13	0.78 (0.38-1.60)	.50	1.08 (0.64-1.84)	.77	1.29 (0.67-2.46)	.45
CMV serostatus								
Negative/negative	Reference		Reference		Reference		Reference	
Other	0.78 (0.30-2.03)	.61	0.92 (0.44-1.93)	.83	0.86 (0.48-1.53)	.61	0.83 (0.40-1.69)	.60
cGVHD before 2-year landmark								
No	Reference		Reference		Reference		Reference	
Yes	2.03 (0.96-4.27)	.06	1.14 (0.65-2.00)	.64	1.38 (0.89-2.14)	.15	1.49 (0.87-2.54)	.15

CMV, cytomegalovirus; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning.
 Bold face values indicate $P < .05$. Variable names are bold.

Long-term NRM remained low at 7% at 5 years from the landmark, consistent with previous analyses outside PT-Cy-based platforms.²³ Infections, GVHD-related complications, and secondary malignancies were the most frequent causes of late nonrelapse death. Although the impact of transplantation and patient characteristics on NRM risk has been studied extensively, their influence on late events after PT-Cy has yet to be established. In this regard, our analyses demonstrate that both patient- and donor-related factors, specifically older patient and donor age and transplantation from a female donor to a male recipient, are associated with an increased risk of late NRM. Notably, the shorter-term relevance of these donor-related factors was already shown in a previous ALWP analysis of PT-Cy-based haploidentical transplantation.¹⁵ Similarly, older donor age and female-to-male transplantation have long been recognized as factors that increase the incidence of GVHD in HLA-matched allo-HSCT.^{23,30-34} Although these associations were validated within the haploidentical cohort, the limited number of events precluded separate analysis of their

impact in the MUD and MSD cohorts. Intriguingly, these associations could not be explained by differences in the proportion of patients entering the analysis with a history of cGVHD or extensive cGVHD, although data on disease activity or severity at the landmark were not available. Additionally, a previous history of cGVHD and an HCT-CI score of ≥3 were associated with a higher risk of late NRM in the subanalysis of the haploidentical cohort. These results suggest that the selection of younger donors, and male donors for male recipients, may significantly affect long-term NRM outcomes when using PT-Cy-based platforms and should be prioritized, when possible, particularly in the setting of haploidentical transplantation.

Relapse risk after allo-HSCT is shaped by the dual selective pressures of the conditioning regimen and graft-versus-leukemia effects. Accordingly, characteristics of the transplantation platform have been associated with both the biology and timing of relapse. For instance, relapse driven by genomic loss of the

mismatched HLA haplotype through copy-neutral loss of heterozygosity occurs frequently after haploidentical transplantation and has been associated with a later onset of relapse.^{24,35} It is conceivable that changes in the immune selective pressures modulated by GVHD prophylaxis, such as the incorporation of PT-Cy, may also influence relapse patterns and dynamics. In this regard, the risk of late relapse in our series was relatively low at 11% at 5 years, a figure comparable with that reported in the ALWP-EBMT study by Larue et al.²³ Importantly, leukemic relapse remained the leading cause of late mortality in this population. Perhaps most notably, we were unable to identify any predictors of late relapse in our multivariate models. Although previous studies have linked the use of haploidentical donors to reduced relapse rates, we did not observe this association in our analysis of late relapse events, suggesting that the protective effect may be limited to the early relapse risk period.¹² Interestingly, neither a history of previous cGVHD, conditioning intensity, nor cytogenetic risk was associated with late relapse risk. Incorporating additional data not fully captured in the registry, such as molecular profiles and peritransplant measurable residual disease status, may help refine our predictive ability. Given these findings, PT-Cy-based allo-HSCT does not appear to result in distinct patterns of late relapse irrespective of donor type, at least in terms of incidence.

Our study has several limitations, primarily related to its registry-based design. First, data on molecular profiles, measurable residual disease status at or after transplant, and details of PT-Cy schedules and dosing were not widely available and could not be included in our analyses. Second, with the notable exception of cGVHD, most late posttransplant events not resulting in death were not captured in the registry, which may have led to underestimation of important clinical outcomes. This is particularly relevant given emerging concerns about PT-Cy-associated toxicities, such as cardiac complications.²⁷⁻²⁹ Third, although restricting the analysis to PT-Cy-based allo-HSCT helped homogenize the study cohorts, the analysis still encompassed a broad range of transplantation platforms that differed in other key characteristics, including conditioning regimens and accompanying GVHD prophylaxis, reflecting underlying variability in real-world clinical practice. Fourth, the low number of late events may have limited our ability to detect associations between patient-, disease-, and transplant-related characteristics and long-term outcomes in multivariate models. Lastly, extended follow-up was unavailable for most patients, limiting the temporal scope of our analyses.

In conclusion, our data reveal relatively low risks of late cGVHD, NRM, and relapse after PT-Cy-based allo-HSCT in patients with

AML who remain leukemia-free 2 years after transplant, with no distinct patterns of late events compared with conventional platforms. Importantly, the degree of HLA matching appeared to have no impact on long-term outcomes, reinforcing the growing role of haploidentical transplantation and the need to refine donor selection based on additional factors in the PT-Cy era.

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Authorship

Contribution: E.R.-A. conceptualized and designed the study, participated in data analysis and interpretation, and wrote the manuscript; A.T.F. performed the statistical analyses; A.M.R., L.M., D.B., J. Versluis, S.S., M.K., L.L.-C., E.N., A.K., S.B., M.R., E.F., M. Martino, J. Vydra, S.P., J.S., M. Mohty, and F.C. contributed to patient recruitment and care, as well as to data acquisition and interpretation; and all authors revised the manuscript critically and gave final approval to submit for publication.

Conflict-of-interest disclosure: E.R.-A. has served as a consultant for Kura Oncology, Syndax Pharmaceuticals, Astellas, Laboratoires Delbert, and Servier; has participated in safety monitoring and steering committees for Kura Oncology; and has received travel support and/or speaker fees from Jazz Pharmaceuticals, Astellas, AbbVie, Gilead, Servier, and Eurocept. The remaining authors declare no competing financial interests.

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