

PTCy-based graft-versus-host disease prophylaxis for matched sibling donor allogeneic hematopoietic cell transplantation

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Key Points

- PTCy-based GVHD prophylaxis was associated with improvement in GRFS, NRM, and OS after MSD PBSC HSCT without increasing relapse risk.
- The addition of ATG to PTCy was associated with an increase in CMV and EBV reactivation without further improving GRFS.

Posttransplant cyclophosphamide (PTCy) is a promising graft-versus-host disease (GVHD) prophylaxis in haploidentical and matched unrelated donor hematopoietic stem cell transplantation (HSCT), but its role in matched sibling donor (MSD) transplants remains unclear. We conducted a retrospective study of 413 MSD-HSCT patients receiving peripheral blood stem cell (PBSC) grafts from January 2010 to January 2023. Patients were categorized into 4 groups: group I (calcineurin inhibitor [CNI] + methotrexate [MTX] or mycophenolate mofetil [MMF]), group II (CNI + MTX or MMF + antithymocyte globulin [ATG]), group III (PTCy + ATG + CNI), and group IV (PTCy + CNI + MMF). PTCy was associated with a significant reduction in grade 2-4 and grade 3-4 acute GVHD and moderate-to-severe chronic GVHD compared with CNI + MTX (or MMF)-containing regimens. PTCy did not increase relapse risk; PTCy reduced nonrelapse mortality, leading to improved GVHD-free/relapse-free survival (GRFS; Hazard Ratio, 0.4; $P < .001$). PTCy was also associated with improved overall survival. Bloodstream infections were increased with PTCy. The addition of ATG to PTCy did not further improve GRFS and was associated with a higher incidence of clinically significant cytomegalovirus (csCMV) and Epstein-Barr virus (csEBV) reactivation and a numerical increase in NRM. PTCy significantly appeared to improve GRFS in the MSD setting using PBSC grafts. The addition of ATG to PTCy increases csCMV and csEBV reactivation without further improving GRFS. Prospective trials and PTCy dose optimization are warranted.

Introduction

Hematopoietic stem cell transplantation (HSCT) has changed greatly with improvements in graft-versus-host disease (GVHD) prophylaxis. However, GVHD still affects 30% to 60% of transplant recipients.¹ GVHD is the leading cause of nonrelapse mortality (NRM).^{2,3} GVHD prophylaxis in matched sibling donor (MSD) transplants has seen limited evolution since the introduction of calcineurin inhibitors (CNIs) combined with methotrexate (MTX) or mycophenolate mofetil (MMF).⁴ Although these regimens continue to be regarded as default options given their strong safety record, chronic GVHD

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Data are available on request from the corresponding author, Arjun Datt Law (arjun.law@uhn.ca).

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

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(cGVHD) remains a significant problem, particularly with the near-universal use of peripheral blood stem cell (PBSC) grafts.^{5,6}

Posttransplant cyclophosphamide (PTCy) was first reported as a safe and effective GVHD prophylaxis strategy in haploidentical transplants and has since been adopted in matched unrelated donor and MSD transplants.⁷ The role of PTCy in MSD transplants remains undecided, given that these transplants are inherently perceived to have lower risks of both acute GVHD (aGVHD) and cGVHD.

PTCy has been associated with high rates of aGVHD when used as a single agent, prompting the exploration of combination strategies.⁸ Regimens combining PTCy with CNIs⁹ or with CNIs and MMF¹⁰ have addressed these issues. The addition of antithymocyte globulin (ATG) to a PTCy-CNI combination has demonstrated significant reduction in both aGVHD and cGVHD.¹¹

In this study, we evaluated the impact of a PTCy-based GVHD prophylaxis strategy compared with 3 other regimens that were used at our center for MSD transplants using PBSC grafts. By comparing these regimens, we aim to provide clearer insights into the efficacy and safety of PTCy within the MSD setting, potentially guiding the development of more effective GVHD prophylaxis strategies for this patient population.

Patients and methods

Patients

All patients undergoing their first HSCT for hematologic malignancies with PBSC grafts from MSDs between January 2010 and January 2023 were included.

Patients were categorized into 4 groups according to the type of GVHD prophylaxis: group I included CNI and either MTX (or MMF); group II included CNI, MTX (or MMF), and ATG; group III included PTCy, ATG, and CNI; and group IV included PTCy, CNI, and MMF. All patients had a minimum post-HSCT follow-up of 12 months.

PTCy was administered IV at a dose of 50 mg/kg on days +3 and +4. The dose of ATG was 0.5 mg/kg on day -3 and 1.5 mg/kg on day -2. Between August 2016 and July 2018, a total of 56 patients (47 with PTCy) received ATG at 0.5 mg/kg on day -3 and 2 mg/kg on days -2 and -1. In groups III and IV, CNI started on day +5. In group IV, MMF was dosed at 15 mg/kg every 8 hours from day +5 to day +35.

Patient-, disease-, and transplant-specific variables were retrieved from electronic medical records. Pre-HSCT fitness was assessed using the Karnofsky performance status (KPS), and comorbidities were assessed using the hematopoietic cell transplantation-specific comorbidity index.¹² The disease risk index (DRI) was documented when applicable.¹³ Transplant-specific variables were recorded, including conditioning regimen, GVHD prophylaxis, stem cell dose, time to neutrophil and platelet engraftment, graft failure, aGVHD and cGVHD, relapse, and death.

Definitions

Complete remission (CR) was defined as per standard criteria, and relapse was defined as the loss of CR.¹⁴ The preparatory regimen was considered myeloablative conditioning (MAC) if the dose of IV busulfan was >6.4 mg/kg or included total body irradiation (TBI) >6 Gy.¹⁵ Neutrophil and platelet engraftment were defined as the first

of 3 consecutive days with an absolute neutrophil count of $\geq 0.5 \times 10^9/L$ and a platelet count of $\geq 20 \times 10^9/L$ without requiring platelet transfusions for 7 consecutive days, respectively. Chimerism was determined by polymerase chain reaction amplification, and full donor chimerism was defined as $\geq 95\%$. Primary graft failure was defined as the failure to reach absolute neutrophil count $\geq 0.5 \times 10^9/L$ by day 28 after HSCT or documentation of autologous reconstitution by chimerism analysis without evidence of disease relapse. Secondary graft failure was defined as a decline in hematopoietic function and donor chimerism after initial engraftment.¹⁶ aGVHD was defined and graded according to the Mount Sinai Acute GVHD International Consortium criteria.¹⁷ Diagnosis and grading of cGVHD was according to the National Institutes of Health 2014 Consensus criteria.¹⁸ Clinically significant Epstein-Barr virus (EBV; csEBV) reactivation was defined as EBV DNA $>3 \times 10^4$ IU/mL in peripheral blood using polymerase chain reaction or the development of EBV⁺ posttransplant lymphoproliferative disorder. Clinically significant cytomegalovirus (CMV; csCMV) reactivation, infection, and disease were defined according to published guidelines.¹⁹

Overall survival (OS) was defined as the time from transplantation to death due to any cause. NRM was defined as death after HSCT not preceded by disease relapse. GVHD-free/relapse-free survival (GRFS) was defined as a composite end point of the occurrence of any of the following: grade 3 to 4 GVHD, cGVHD requiring systemic treatment, relapse, or death, whichever occurred earlier.²⁰

Statistical analysis

Continuous variables were summarized as median and either range or interquartile range (IQR; 25th and 75th percentiles). Comparisons between groups were conducted using the Mann-Whitney *U* test. Categorical variables were reported as absolute numbers and percentages, with comparisons made using the χ^2 test.

The primary clinical outcomes of interest included aGVHD, cGVHD, NRM, GRFS, relapse, and OS. The secondary outcomes included time to neutrophil and platelet engraftment, rates of CMV and EBV reactivation, and bloodstream infections (BSIs).

OS and GRFS were estimated using the Kaplan-Meier method, and the differences between groups were assessed with the log-rank test. Median follow-up was determined using the reversed Kaplan-Meier method. The cumulative incidence of relapse and NRM were analyzed within a competing risks framework considering NRM as a competing risk for relapse and death as a competing risk for relapse. This competing risk approach was also applied for the estimation of aGVHD and cGVHD, with relapse and death before GVHD onset treated as competing events. The cumulative incidence rates for neutrophil and platelet engraftment, CMV, EBV reactivation, and bloodstream BSI were also computed using the competing risks framework.

Univariate analyses are presented in the supplement (Tables 1-3). Multivariable analyses (MVAs) were performed using Cox proportional hazards regression models for OS and GRFS. For NRM and relapse, Fine-Gray hazard models were used. We constructed 2 models for MVAs: the first compared outcomes across the 4 groups, whereas the second specifically compared groups III and IV to determine whether the addition of ATG to the PTCy backbone influenced the outcomes of interest. The variables

Table 1. Baseline characteristics

	All (N = 413)	Group I CNI-MTX (or MMF) (n = 210)	Group II ATG-CNI-MTX (n = 34)	Group III PTCy-ATG-CNI (n = 78)	Group IV PTCy-CNI- MMF (n = 91)	P value
Age, median (IQR), y						
Recipient	56 (44-63)	55 (45-62)	58 (38-65)	57 (47-63)	56 (43-63)	.92
Donor	54 (44-61)	53 (45-61)	52 (33-60)	55 (44-61)	55 (42-62)	.20
Patient sex, male, n (%)	217	109 (51.9)	21 (61.8)	44 (56.4)	43 (47.3)	.44
Donor-recipient sex, n (%)						
Male-male	110 (26.6)	62 (29.5)	8 (23.5)	17 (21.8)	23 (25.3)	
Male-female	94 (22.8)	52 (24.8)	4 (11.8)	16 (20.5)	22 (24.2)	.30
Female-male	107 (25.9)	47 (22.4)	13 (38.2)	27 (34.6)	20 (22)	
Female-female	102 (24.7)	49 (23.3)	9 (26.5)	18 (23.1)	26 (28.6)	
Diagnosis, n (%)						
Acute myeloid leukemia	224 (54.2)	116 (55.2)	16 (47.1)	44 (56.4)	48 (52.7)	
Myelodysplastic syndrome	63 (15.3)	30 (14.3)	5 (14.7)	13 (16.7)	15 (16.5)	
Myelofibrosis	39 (9.4)	22 (10.5)	4 (11.8)	10 (12.8)	3 (3.3)	
Chronic myeloid leukemia	19 (4.6)	12 (5.7)	1 (2.9)	1 (1.3)	5 (5.5)	
Chronic myelomonocytic leukemia	11 (2.7)	5 (2.4)	1 (2.9)	1 (1.3)	4 (4.4)	.18
Acute lymphoblastic leukemia	48 (11.6)	25 (11.9)	6 (17.6)	5 (6.4)	12 (13.2)	
Others	9 (2.2)	0 (0.0)	1 (2.9)	4 (5.1)	4 (4.4)	
Remission status at HSCT, n (%)						
CR1	349 (84.5)	182 (86.7)	24 (70.6)	68 (87.2)	75 (82.4)	
CR >2	57 (13.8)	28 (13.3)	9 (26.5)	7 (9.0)	13 (14.3)	.06
Active disease	7 (1.7)	0 (0.0)	1 (2.9)	3 (3.8)	3 (3.3)	
DRI, n (%)						
Low	6 (1.5)	3 (1.4)	1 (2.9)	0	2 (2.2)	
Intermediate	203 (49.2)	89 (42.4)	19 (55.9)	41 (52.6)	54 (59.3)	.12
High	133 (32.2)	81 (38.6)	9 (26.5)	25 (32.1)	18 (19.8)	
Very high	71 (17.2)	37 (17.6)	5 (14.7)	12 (15.4)	17 (18.7)	
Performance status, KPS <80, n (%)	89 (21.5)	50 (24.0)	7 (20.6)	17 (21.8)	15 (16.5)	.54
HCT-CI score ≥3, n (%)	131 (31.7)	71 (33.8)	11 (32.4)	21 (26.9)	28 (30.8)	.58
Conditioning intensity, n (%)						
Reduced intensity	215 (52%)	82 (39.0)	18 (52.9)	72 (92.3)	43 (47.3)	<.01
Myeloablative	198 (48%)	128 (61.0)	16 (47.1)	6 (7.7)	48 (52.7)	
TBI received, n (%)	350 (84.5)	206 (98.1)	22 (64.7)	75 (96.2)	47 (51.6)	<.01
ABO status, n (%)						
Compatible	259 (62.8)	131 (62.4)	18 (52.9)	45 (57.7)	65 (71.4)	
Bidirectional incompatibility	23	11 (5.2)	2 (5.9)	3 (3.8)	7 (7.7)	.12
Major incompatibility	71	33 (15.7)	11 (32.4)	17 (21.8)	10 (11.0)	
Minor incompatibility	60	35 (16.7)	3 (8.8)	13 (16.7)	9 (9.9)	
CMV serostatus, n (%)						
D+/R+	230 (55.7)	125 (59.5)	14 (41.2)	39 (50.0)	52 (57.1)	
D+/R-	39 (9.4)	22 (10.5)	2 (5.9)	8 (10.3)	7 (7.7)	.97
D-/R+	86 (20.8)	34 (16.2)	13 (38.2)	19 (24.4)	20 (22.0)	
D-/R-	58 (14.1)	29 (13.8)	5 (14.7)	12 (15.4)	12 (13.2)	
Letermovir primary prophylaxis, n (%)	15 (3.6)	0	15 (3.6)	0	0	<.01
Cryopreserved graft, n (%)	201 (48.7)	141 (67.1)	7 (20.6)	50 (64.1)	3 (3.3)	<.01
CD34 ⁺ cell dose median (IQR), ×10 ⁶ /kg	6.8 (4.9-8.3)	6.1 (4.4-8.5)	6.8 (4.1-7.3)	7.6 (5.4-10.7)	7 (5.8-8)	.83

ABO, blood group; CR1, first complete remission; D+, seropositive donor; D-, seronegative donor; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; R+, seropositive recipient; R-, seronegative recipient.

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Table 2. Multivariable analysis across all 4 groups

Variable	Group I	Group II	Group III	Group IV
	CNI-MTX (n = 210)	ATG-CNI-MTX (n = 34)	PTCy-ATG-CNI (n = 78)	PTCy-CNI- MMF (n = 91)
OS	Ref	0.9 (0.5-1.5); <i>P</i> = .75	0.6 (0.3-0.8); <i>P</i> = .01	0.5 (0.3-0.9); <i>P</i> = .01
GRFS	Ref	0.6 (0.4 -1.1); <i>P</i> = .14	0.4 (0.3-0.6); <i>P</i> < .01	0.4 (0.2-0.6); <i>P</i> < .01
NRM	Ref	0.6 (0.3-1.4); <i>P</i> = .3	0.4 (0.2-0.8); <i>P</i> = .01	0.3 (0.1-0.6); <i>P</i> < .01
aGVHD grade 2-4	Ref	0.6 (0.4-1.2); <i>P</i> = .1	0.4 (0.2-0.7); <i>P</i> < .01	0.6 (0.4-0.9); <i>P</i> = .01
aGVHD grade 3-4	Ref	0.3 (0.1 -1.2); <i>P</i> = .1	0.3 (0.1- 0.8); <i>P</i> = .01	0.2 (0.1 - 0.6); <i>P</i> < .01
cGVHD	Ref	0.2 (0.1-0.5); <i>P</i> < .01	0.3 (0.2-0.4); <i>P</i> < .01	0.5 (0.4-0.7); <i>P</i> < .01
cGVHD moderate to severe	Ref	0.1 (0.1-0.5); <i>P</i> < .01	0.2 (0.1-0.3); <i>P</i> < .01	0.4 (0.2-0.6); <i>P</i> < .01
BSIs	Ref	0.9 (0.5-1.7); <i>P</i> = .9	1.6 (1.2-2.5); <i>P</i> < .01	1.5 (1.3-2.3); <i>P</i> < .01

included in the MVA models were KPS <90 (vs ≥90), conditioning regimen intensity (reduced-intensity conditioning [RIC] vs MAC), GVHD prophylaxis groups (groups I vs II, III, and IV for the first MVA model; group III vs IV for the second MVA model), cryopreservation (vs fresh), DRI (high or very high vs others), CMV seropositive recipient (vs negative). Clinically significant variables with *P* values <.1 in the univariate analysis were included in the MVA. All *P* values were 2 sided, and *P* value <.05 was considered statistically significant. Statistical analyses were performed using Easy R (version 1.62, Saitama Medical Center, Jichi Medical University, Saitama, Japan).²¹ The study was approved by the institutional ethics committee, University Health Network, Toronto.

Results

Patient and transplantation characteristics

Between January 2010 and 2023, a total of 413 patients underwent MSD-HSCT. The institutional GVHD prophylaxis regimen evolved during the study period, and in October 2015, PTCy was included as the standard GVHD prophylaxis backbone for all donor types.

The GVHD prophylaxis included CNI and MTX (or MMF) in 210 patients (51%; group I). CNI and MTX (or MMF) in combination with ATG was used in 34 (8%; group II). ATG in combination with PTCy and CNI was used for 78 patients (19%; group III), and 91

(22%) received PTCy in combination with CNI and MMF (group IV). The median follow-up was 39 months (range, 9-98) for group I, 25 months (range, 13-36) for group II, 46 months (range, 8-61) for group III, and 15 months (range, 9-28) for group IV.

The median age at HSCT was 56 years (IQR, 44-63), and 196 (47.5%) were female. The median age of the sibling donors was 54 years (IQR, 44-61). One hundred and seven males (25.9%) received grafts from female donors. Acute myeloid leukemia was the most common indication (54.2%). Most patients were in first complete remission (84.5%). The DRI was high/very high in 204 patients (49.4%). The median KPS of the cohort was 90 (range, 60-100), and 141 (34.2%) had an hematopoietic cell transplantation-specific comorbidity index score of ≥3. RIC was used in 215 patients (52%), and 350 (84.5%) received TBI. The median CD34⁺ cell dose was 6.8 × 10⁶/kg (range, 4.9 × 10⁶/kg to 8.3 × 10⁶/kg). Cryopreserved grafts were used in 201 patients (48.7%). Fifteen patients (3.6%) received letemovir for CMV prophylaxis.

Baseline characteristics were comparable between the 4 groups, except in terms of conditioning regimen intensity, TBI, and cryopreserved graft use (Table 1).

Engraftment and chimerism

At day +28, the cumulative incidence of neutrophil engraftment was 98.1% (95% confidence interval [CI], 96-99) for the cohort. The median time to neutrophil engraftment was delayed in patients receiving PTCy, and it was 15 days in group I, 14 days in group II, 16 days in group III, and 18 days in group IV (*P* = .03; supplemental Figure 1A).

At day +28 and day +60, the cumulative incidence of platelet engraftment was 83.7% (95% CI, 80-87) and 88.3% (95% CI, 84.8-91.1), respectively. The median time to platelet engraftment was also delayed in patients receiving PTCy, and it was 12 days for groups I and II vs 15 days for groups III and IV (*P* = .04; supplemental Figure 1B).

Full donor chimerism at day +30 was achieved by 268 of 300 evaluable patients (89.3%). There was no difference in the attainment of full donor chimerism between the groups (*P* = .18).

Primary graft failure occurred in 3 patients. There were no primary graft failures in patients receiving PTCy. Four patients experienced secondary graft failure at a median of 362 days (range, 132-690) after HSCT. Three of these patients received a combination of

Table 3. Multivariable analysis comparing PTCy with and without ATG

Variable	Group III	Group IV
	PTCy-ATG-CNI (n = 78)	PTCy-CNI-MMF (n = 91)
OS	1.4 (0.8-2.4); <i>P</i> = .19	Ref
GRFS	0.9 (0.6-1.5); <i>P</i> = .96	Ref
NRM	1.7 (0.7-4.4); <i>P</i> = .2	Ref
aGvHD grade 2-4	0.7 (0.4-1.2); <i>P</i> = .23	Ref
aGvHD grade 3-4	1.1 (0.2-3.8); <i>P</i> = .94	Ref
cGvHD	0.5 (0.3-0.9); <i>P</i> = .02	Ref
cGvHD moderate to severe	0.4 (0.2-0.8); <i>P</i> < .01	Ref
BSIs	1.1 (0.7-1.5); <i>P</i> = .81	Ref
csCMV	2.1 (1.3-3.5); <i>P</i> < .01	Ref
csEBV	9.5 (2.8-31.2); <i>P</i> < .01	Ref

ATG, PTCy, and CNI (group III) for GVHD prophylaxis and had csEBV reactivation requiring treatment with rituximab.

GVHD

A total of 234 patients (56.6%) developed aGVHD at a median of 56 days (range, 17-180). Grade 2 to 4 aGVHD was documented in 182 patients (77.7%) and grade 3 to 4 in 57 patients (24.3%). The skin was the most commonly affected organ (74.3%), followed by the gastrointestinal tract (45.7%).

At day +100, the cumulative incidence of grade 2 to 4 aGVHD was 33.3% (95% CI, 28.7-38) and was significantly reduced in patients receiving PTCy ± ATG; 40.6% in group I, 30.6% in group II, 16% in group III, and 32% in group IV ($P < .001$; Figure 1A). The day +100 cumulative incidence of grade 3 to 4 aGVHD was 10.5% (95% CI, 7.5-14). Patients receiving PTCy ± ATG (groups III and IV) had a significantly lower risk of developing grade 3 to 4 aGVHD; 17.4% in group I, 3.7% in group II, 3.1% in group III, and 5.1% in group IV ($P < .001$; Figure 1B).

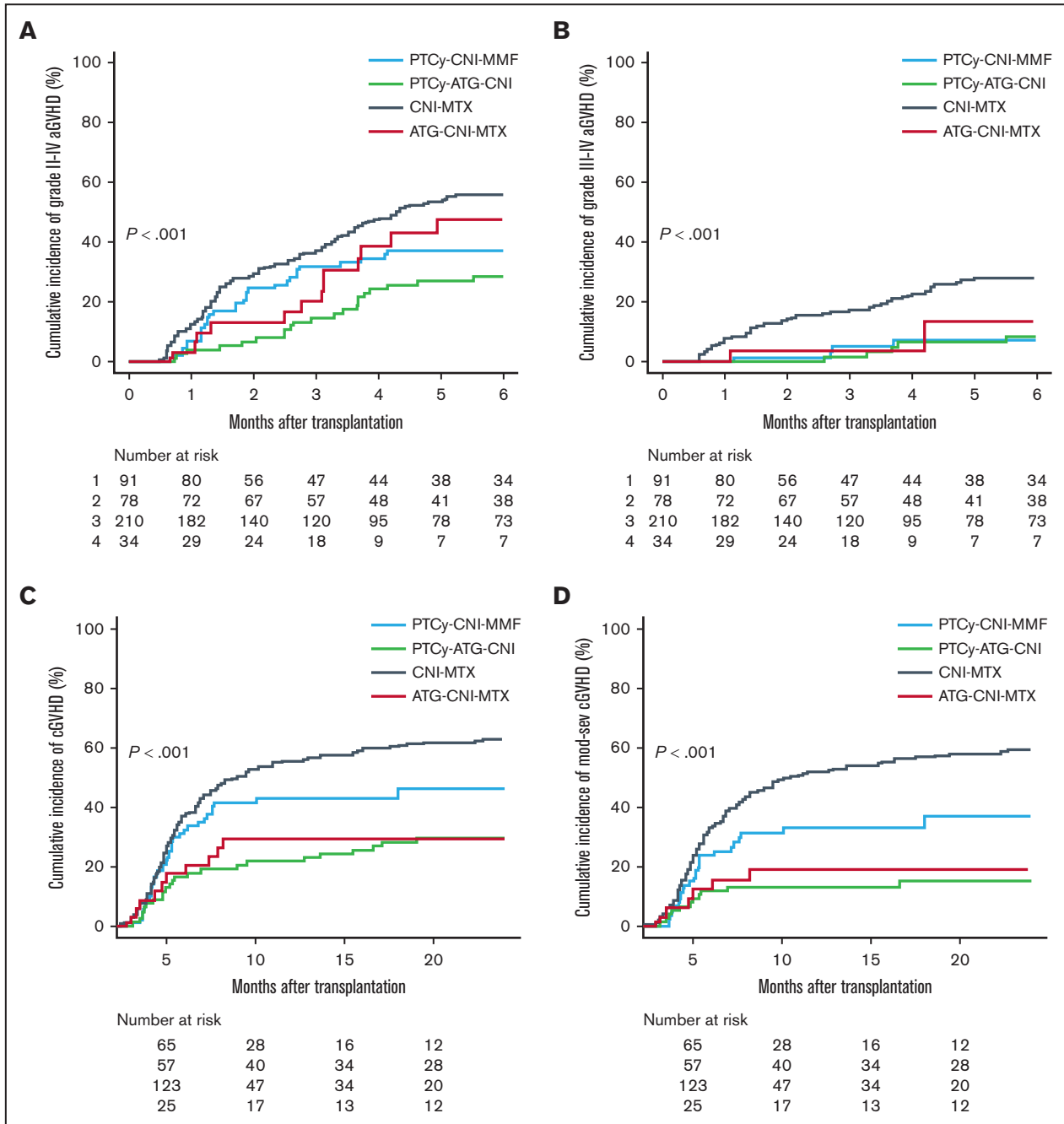


Figure 1. Incidence of varying degrees of acute and chronic GVHD across different forms of GVHD prophylaxis. (A) Cumulative incidence of grade 2 to 4 aGVHD. (B) Cumulative incidence of grade 3 to 4 aGVHD. (C) Cumulative incidence of all-grade cGVHD. (D) Cumulative incidence of moderate-to-severe (mod-sev) cGVHD.

At 12 months, the cumulative incidence of all grades of cGVHD was 44.7% (95% CI, 39.8-49.5) and was significantly higher for patients in group I (55.7%) than those in groups II, III, and IV (29.4%, 21.8%, and 43.1%, respectively; $P < .001$; Figure 1C).

The cumulative incidence of moderate-severe cGVHD at 12 months was 38.2% (95% CI, 33.3-43.1); 52% in group I, 18.9% in group II, 13.3% in group III, and 33.1% in group IV ($P < .001$; Figure 1D).

In patients without aGVHD or cGVHD, the median time to discontinue immunosuppression was 96 days (range, 91-99) in patients receiving PTCy and 128 days (range, 114-140) in others ($P = .15$).

GRFS

The composite end point of GRFS at 1 year and 2 years was 58.1% (95% CI, 48.4-66.7) and 51.1% (95% CI, 40.3-60.9), respectively. The 1-year GRFS was 15.1% in group I, 50% in group II, 50% in group III, and 49.1% in group IV ($P < .001$; (Figure 2B).

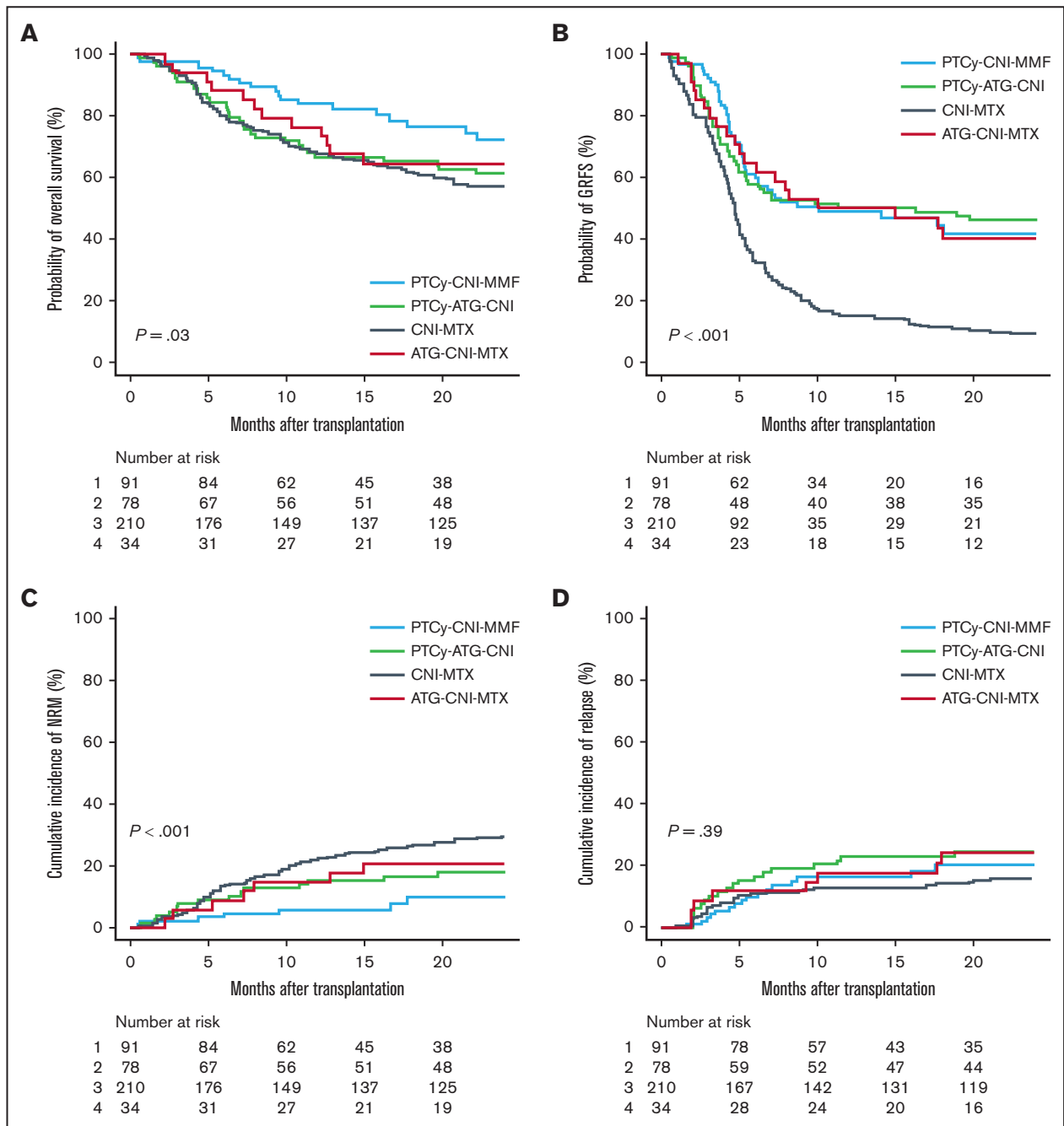


Figure 2. Comparison of posttransplant outcomes according to type of GVHD prophylaxis. (A) OS. (B) GRFS. (C) Cumulative incidence of NRM. (D) Cumulative incidence of relapse.

On univariate analysis, the use of ATG (hazard ratio [HR], 0.61; $P < .01$), PTCy (HR, 0.37; $P < .01$), and high/very high DRI (HR, 1.3; $P = .03$) influenced GRFS.

Relapse, NRM, and OS

Eighty-eight patients (21.3%) relapsed at a median of 6 months (IQR, 2.9-16.5) after HSCT. The cumulative incidence of relapse did not differ between the 4 groups ($P = .39$; Figure 2D). The use of PTCy did not increase the risk of relapse on univariable analysis ($P = .4$). On MVA, high/very high DRI was the only factor predictive of relapse (HR, 1.78; 95% CI, 1.15-2.75; $P = .009$; Table 2).

Infection (38.3%) and GVHD (35.8%) were the most common causes of NRM. At day +100 and day +365, the cumulative incidence of NRM was 4.4% (95% CI, 2.7-6.6) and 16.8% (95% CI, 13.3-20.6), respectively. The use of PTCy resulted in increased day +30 NRM (2.2% vs 0.5%; $P < .001$). However, at day +100, the NRM was 4.3% in group I, 5.9% in group II, 6.4% in group III, and 2.2% in group IV ($P < .001$; Figure 2C). The NRM at 1 and 2 years after HSCT was also significantly improved in patients receiving PTCy (5.9% [95% CI, 2.2-12.4] and 9.8% [95% CI, 4.1-18.5], respectively).

At a median follow-up of 54 months (IQR, 25-96) for survivors, 213 patients (51.6%) were alive. The median OS of the cohort was 59.3 months (95% CI, 44-87), and the 2-year OS was 61.4% (95% CI, 56.3-66). The 2-year OS was higher in patients receiving PTCy; 56.6% in group I, 64.6% in group II, 61.4% in group III, and 72.4% in group IV ($P = .03$; Figure 2A).

Infections

There were 144 episodes of csCMV reactivation. The median time from HSCT to csCMV reactivation was 37 days (range, 15-55). Eleven patients (7.6%) developed CMV disease, and 8 (5.5%) died of CMV-related organ damage (colitis, $n = 5$; pneumonia, $n = 3$). All deaths due to CMV pneumonitis occurred in the group receiving CNI-MTX (or MMF). Among the 5 patients with CMV colitis, 3 belonged to the CNI-MTX (or MMF) group, whereas 2 were in the ATG-PTCy-CNI group.

The day +100 cumulative incidence of csCMV reactivation was 29% in group I, 11.8% in group II, 42.3% in group III, and 22% in group IV ($P = .004$; supplemental Figure 2A).

Thirty-seven patients developed csEBV reactivation at a median of 71 days (range, 24-285) after HSCT. The day +100 cumulative incidence of csEBV reactivation was 1.4% in group I, 17.6% in group II, 23.1% in group III, and 2.2% in group IV ($P = .001$; supplemental Figure 2B). Three patients (0.7%) developed posttransplant lymphoproliferative disorder and were treated with rituximab.

There were 195 documented BSIs (47.2%). Most patients developed BSI during the first 60 days ($n = 119$ [61%]). The majority had gram-positive BSI ($n = 111$ [57%]). At day +100, the cumulative incidence of BSI was 22.4% in group I, 29.4% in group II, 48.7% in group III, and 46.2% in group IV ($P < .001$; supplemental Figure 2C).

MVA

We developed a multivariable model to account for the influence of confounding variables on clinically significant outcomes. Clinically significant variables with P value $< .1$ in the univariate analysis were included in the MVA (Table 2). The use of PTCy was associated with a reduced risk of grade 2 to 4 aGVHD (HR, 0.6; 95% CI, 0.3-0.9; $P = .01$) and grade 3 to 4 aGVHD (HR, 0.2; 95% CI, 0.1-0.6; $P < .01$). PTCy was also associated with a reduced risk of all-grade cGVHD (HR, 0.5; 95% CI, 0.4-0.7; $P < .01$) and moderate-severe cGVHD (HR, 0.4; 95% CI, 0.2-0.6; $P < .01$). High/very high DRI was the only factor predictive of relapse (HR, 1.78; 95% CI, 1.15-2.75; $P = .009$). PTCy was associated with a significantly reduced risk of NRM (HR, 0.3; 95% CI, 0.2-0.7; $P = .002$).

Consequently, the use of PTCy was associated with significantly improved GRFS (HR, 0.4; 95% CI, 0.2-0.6; $P < .001$) and OS (HR, 0.56; 95% CI, 0.4-0.9; $P = .01$). PTCy-based regimens were associated with a statistically significant increase in BSI (HR, 1.5; 95% CI, 1.2-2.1; $P = .001$).

We conducted another MVA to evaluate whether the addition of ATG to the PTCy backbone influenced key outcomes (Table 3). The addition of ATG to PTCy did not result in a significant reduction in the incidence of grade 2 to 4 or grade 3 to 4 aGVHD. However, it was associated with a lower incidence of both all-grade and moderate-to-severe cGVHD. There was no significant improvement in GRFS, NRM, or OS with the addition of ATG. The addition of ATG to PTCy led to an increase in csCMV and csEBV but not BSI.

Causes of death

At the last follow-up, 200 patients (48.4%) in the cohort died. The causes of death among the 4 groups are shown in Table 4. Deaths attributed to GVHD and its treatment were more common in patients receiving CNI and MTX (or MMF). There were no deaths attributed to cardiac toxicity in patients receiving PTCy.

Discussion

Fully matched siblings remain the preferred donor choice for allogeneic HSCT, when available.²² The traditional GVHD prophylaxis regimen in MSD-HSCT, comprising CNI and MTX, was established

Table 4. Cause of death

n (%)	All (N = 413)	Group I		Group II		Group III		Group IV	
		CNI-MTX (n = 210)	ATG-CNI-MTX (n = 34)	PTCy-ATG-CNI (n = 78)	PTCy-CNI- MMF (n = 91)				
Relapse	86 (43)	39 (45.4)	12 (13.9)	20 (23.3)	15 (17.4)				
Infections	54 (27)	31 (57.4)	6 (11.1)	13 (24.1)	4 (7.4)				
GVHD	45 (22.5)	33 (73.3)	6 (13.3)	5 (11.1)	1 (2.2)				
Cardiac events	9 (4.5)	9 (100)	0	0	0				
Veno-occlusive disease	6 (3)	3 (50)	0	2 (33.3)	1 (16.7)				

in the 1980s when bone marrow was the predominant graft source.⁴ With the near-universal shift toward granulocyte colony stimulating factor–mobilized PBSC grafts, the ongoing utility of this combination, particularly in the face of rapid innovations in unrelated donor transplants, is being questioned. PTCy is increasingly used for GVHD prophylaxis beyond the haploidentical transplant setting. The BMT CTN 1203 trial, which evaluated different GVHD prophylaxis regimens, did not separately report outcomes for MSD and matched unrelated donor transplants, leaving questions about the specific advantages of PTCy in MSD transplants unresolved.²³ Similarly, the BMT CTN 1703 study examined the outcomes of patients undergoing HLA-matched transplants with RIC, limiting the cohort to older patients.²⁴

Despite its benefits, PTCy as a single agent is associated with high rates of severe GVHD.⁸ To mitigate this, PTCy is frequently combined with additional immunosuppressive agents, although these combinations have yet to be evaluated in randomized trials within the MSD context.^{11,25,26}

In our large retrospective study, we examined the outcomes of patients receiving PBSC grafts from MSD with GVHD prophylaxis regimens developed around a PTCy backbone. We compared these outcomes with those of patients treated with the legacy CNI and MTX (or MMF) regimen. Consistent with previously reported results, our findings demonstrate that PTCy combined with CNI and MMF (or ATG and CNI) significantly reduces the incidence of grade 2 to 4 and grade 3 to 4 aGVHD without affecting relapse rates.²⁵

The use of PTCy has been associated with reduced rates of cGVHD across donor types.^{27,28} This is largely driven by the selective depletion of activated alloreactive T lymphocytes by PTCy.²⁹ In our study, we observed a similar reduction in all grades of cGVHD, consistent with previous findings in the MSD setting.^{30,31}

Despite concerns that adding immunosuppressive agents might diminish the graft-versus-leukemia effect and increase relapse risk, this was not seen in our study. MVA identified a high/very high DRI as the only factor associated with relapse. Similarly, previous studies with PTCy combinations in the MSD setting have not demonstrated an increased relapse risk.^{25,30,31}

PTCy-based GVHD prophylaxis has been associated with an increased incidence of BSI.^{32,33} In our study, patients receiving PTCy had a 1.5× higher risk of developing BSI. Most BSIs were diagnosed before day +60. This could explain the observed increase in the day +30 NRM in patients receiving PTCy in our study. However, NRM at day +100 and 1 and 2 years were reduced with PTCy, suggesting improved longer-term outcomes. In a study that predominantly included patients with acute leukemia receiving MAC, Kwon et al reported a significantly improved 2-year NRM in patients receiving PTCy compared with cyclosporine-methotrexate (8.8% vs 24%; $P = .05$). Similar to our findings, most NRM events in the cyclosporine-methotrexate group were secondary to GVHD.²⁵

The use of ATG in the MSD setting remains controversial. The European Society of Blood and Marrow Transplantation guidelines recommend considering rabbit ATG in MSD-HSCT patients at high risk of GVHD.³⁴ However, ATG is associated with delayed immune reconstitution and consequently leads to an increased risk of infections, particularly viral reactivation after HSCT.^{35,36} In our

study, patients who received ATG in combination with PTCy experienced a significant increase in CMV and EBV reactivation. The combination of ATG and PTCy also led to an increase in NRM, driven primarily by a rise in infection-related deaths; however, this increase was not statistically significant. Notably, the addition of ATG to PTCy did not increase the incidence of BSI.

In our study, CMV-related end organ damage and mortality were higher in patients receiving CNI-MTX (or MMF). Despite the increased rate of CMV reactivation, CMV-related mortality has decreased in the contemporary era due to the widespread adoption of letermovir for primary prophylaxis, the availability of newer antivirals such as maribavir, and improved supportive care practices.^{37,38}

In our study, patients receiving PTCy showed a significant improvement in the composite end point of GRFS, driven by a reduction in both aGVHD and cGVHD without an associated increase in relapse risk. These findings are consistent with previous reports demonstrating that PTCy significantly appeared to improve GRFS by reducing the incidence of severe GVHD.^{25,31} We did not see any additional benefit from the inclusion of ATG to a PTCy-based regimen, in contrast to the improved outcomes demonstrated with other donor types.³⁹⁻⁴¹

Consistent with previous studies, PTCy was associated with slower neutrophil and platelet engraftment.^{11,25,31} This delay did not lead to increased graft failure. Additionally, donor chimerism was not affected by the use of PTCy.

High doses of PTCy have been associated with increased BSIs, cardiac toxicity, and an increase in early NRM.⁴² Our study did not show an increased incidence of cardiac events in the PTCy group compared with the CNI/MTX (MMF) group. Recent developments suggest that further optimizing the PTCy dose in selected individuals could mitigate toxicity without compromising its efficacy in preventing GVHD.⁴³

The primary limitations of our study include its retrospective design and the heterogeneity of the underlying diagnoses. The temporal discrepancy between cohorts may have also introduced bias into our findings. The small number of patients receiving ATG in combination with CNI and MTX further limited our ability to draw definitive conclusions. Additionally, we lacked granular data on immune reconstitution to compare the kinetics between groups. Due to the limited number of patients, we were also unable to explore the impact of letermovir on CMV reactivation. Prospective studies are necessary to validate these findings and determine the optimal GVHD prophylaxis regimen for MSD transplants, particularly when considering additional variables such as conditioning intensity.

In conclusion, our study demonstrates the utility and efficacy of PTCy-based GVHD prophylaxis strategy in MSD-HSCT in a contemporary setting and shows a significant improvement in clinically meaningful outcomes such as GRFS compared with legacy CNI-MTX (or MMF)–based protocols. Further studies including prospective trials and advances in dose optimization are necessary.

Authorship

Contribution: N.D. and A.D.L. conceptualized and designed the study; N.D. and M.R. performed statistical analysis; and all authors reviewed the manuscript.

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References

- Holtan SG, Yu J, Choe HK, et al. Disease progression, treatments, hospitalization, and clinical outcomes in acute GVHD: a multicenter chart review. *Bone Marrow Transplant.* 2022;57(10):1581-1585.
- Solomon SR, Bachier-Rodriguez L, Bashey A, et al. Impact of graft-versus-host disease on relapse and nonrelapse mortality following posttransplant cyclophosphamide-based transplantation. *Transplant Cell Ther.* 2024;30(9):903.e1-903.e9.
- DeFilipp Z, Alousi AM, Pidala JA, et al. Nonrelapse mortality among patients diagnosed with chronic GVHD: an updated analysis from the Chronic GVHD Consortium. *Blood Adv.* 2021;5(20):4278-4284.
- Storb R, Deeg HJ, Whitehead J, et al. Methotrexate and cyclosporine compared with cyclosporine alone for prophylaxis of acute graft versus host disease after marrow transplantation for leukemia. *N Engl J Med.* 1986;314(12):729-735.
- Bensinger WI. Allogeneic transplantation: peripheral blood versus bone marrow. *Curr Opin Oncol.* 2012;24(2):191-196.
- Friedrichs B, Tichelli A, Bacigalupo A, et al. Long-term outcome and late effects in patients transplanted with mobilised blood or bone marrow: a randomised trial. *Lancet Oncol.* 2010;11(4):331-338.
- Luznik L, O'Donnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. *Biol Blood Marrow Transplant.* 2008;14(6):641-650.
- Bradstock KF, Bilmon I, Kwan J, et al. Single-agent high-dose cyclophosphamide for graft-versus-host disease prophylaxis in human leukocyte antigen-matched reduced-intensity peripheral blood stem cell transplantation results in an unacceptably high rate of severe acute graft-versus-host disease. *Biol Blood Marrow Transplant.* 2015;21(5):941-944.
- Mielcarek M, Furlong T, O'Donnell PV, et al. Posttransplantation cyclophosphamide for prevention of graft-versus-host disease after HLA-matched mobilized blood cell transplantation. *Blood.* 2016;127(11):1502-1508.
- Nagler A, Labopin M, Swoboda R, et al. Post-transplant cyclophosphamide, calcineurin inhibitor, and mycophenolate mofetil compared to anti-thymocyte globulin, calcineurin inhibitor, and methotrexate combinations as graft-versus-host disease prophylaxis post allogeneic stem cell transplantation from sibling and unrelated donors in patients with acute myeloid leukemia: a study on behalf of the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *Bone Marrow Transplant.* 2024;59(7):1012-1021.
- Kunacheewa C, Owattanapanish W, Jirabanditsakul C, Issaragrisil S. Post-transplant cyclophosphamide and thymoglobulin, a graft-versus-host disease prophylaxis in matched sibling donor peripheral blood stem cell transplantations. *Cell Transplant.* 2020;29:0963689720965900.
- Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood.* 2005;106(8):2912-2919.
- Armand P, Gibson CJ, Cutler C, et al. A disease risk index for patients undergoing allogeneic stem cell transplantation. *Blood.* 2012;120(4):905-913.
- Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood.* 2022;140(12):1345-1377.
- Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. *Biol Blood Marrow Transplant.* 2009;15(12):1628-1633.
- Kharfan-Dabaja MA, Kumar A, Ayala E, et al. Standardizing definitions of hematopoietic recovery, graft rejection, graft failure, poor graft function, and donor chimerism in allogeneic hematopoietic cell transplantation: a report on behalf of the American Society for Transplantation and Cellular Therapy. *Transplant Cell Ther.* 2021;27(8):642-649.
- Harris AC, Young R, Devine S, et al. International, multicenter standardization of acute graft-versus-host disease clinical data collection: a report from the Mount Sinai Acute GVHD International Consortium. *Biol Blood Marrow Transplant.* 2016;22(1):4-10.
- Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 Diagnosis and Staging Working Group Report. *Biol Blood Marrow Transplant.* 2015;21(3):389-401.e1.
- Ljungman P, Boeckh M, Hirsch HH, et al; Disease Definitions Working Group of the Cytomegalovirus Drug Development Forum. Definitions of cytomegalovirus infection and disease in transplant patients for use in clinical trials. *Clin Infect Dis.* 2017;64(1):87-91.
- Holtan SG, DeFor TE, Lazaryan A, et al. Composite end point of graft-versus-host disease-free, relapse-free survival after allogeneic hematopoietic cell transplantation. *Blood.* 2015;125(8):1333-1338.
- Kanda Y. Investigation of the freely available easy-to-use software 'EZ' for medical statistics. *Bone Marrow Transplant.* 2013;48(3):452-458.

22. Holtan SG, Versluis J, Weisdorf DJ, Cornelissen JJ. Optimizing donor choice and GVHD prophylaxis in allogeneic hematopoietic cell transplantation. *J Clin Oncol*. 2021;39(5):373-385.
23. Bolaños-Meade J, Reshef R, Fraser R, et al. Three prophylaxis regimens (tacrolimus, mycophenolate mofetil, and cyclophosphamide; tacrolimus, methotrexate, and bortezomib; or tacrolimus, methotrexate, and maraviroc) versus tacrolimus and methotrexate for prevention of graft-versus-host disease with haemopoietic cell transplantation with reduced-intensity conditioning: a randomised phase 2 trial with a non-randomised contemporaneous control group (BMT CTN 1203). *Lancet Haematol*. 2019;6(3):e132-e143.
24. Bolaños-Meade J, Hamadani M, Wu J, et al; BMT CTN 1703 Investigators. Post-transplantation cyclophosphamide-based graft-versus-host disease prophylaxis. *N Engl J Med*. 2023;388(25):2338-2348.
25. Kwon M, Bailén R, Pascual-Cascón MJ, et al. Posttransplant cyclophosphamide vs cyclosporin A and methotrexate as GVHD prophylaxis in matched sibling transplantation. *Blood Adv*. 2019;3(21):3351-3359.
26. Shouman MT, Mansour OM, El Gammal MM, et al. Post-transplantation cyclophosphamide-based graft-versus-host-disease prophylaxis compared to methotrexate-cyclosporine a in matched-related allogeneic hematopoietic stem cell transplantation. *Hematol Oncol Stem Cell Ther*. 2023;16(4):379-387.
27. Maurer K, Ho VT, Inyang E, et al. Posttransplant cyclophosphamide vs tacrolimus-based GVHD prophylaxis: lower incidence of relapse and chronic GVHD. *Blood Adv*. 2023;7(15):3903-3915.
28. Ahmed S, Kanakry JA, Ahn KW, et al. Lower graft-versus-host disease and relapse risk in post-transplant cyclophosphamide-based haploidentical versus matched sibling donor reduced-intensity conditioning transplant for Hodgkin lymphoma. *Biol Blood Marrow Transplant*. 2019;25(9):1859-1868.
29. Cutler CS, Koreth J, Ritz J. Mechanistic approaches for the prevention and treatment of chronic GVHD. *Blood*. 2017;129(1):22-29.
30. Shouman M, Mansour O, Gammal MME, Abdel-Fattah R, Samra MA, Haddad AE, et al. Post-transplantation cyclophosphamide based graft-versus-host-disease prophylaxis compared to methotrexate-cyclosporine A in matched related allogeneic hematopoietic stem cell transplantation. *Hematol Oncol Stem Cell Ther*. 2023;16(4):379-387.
31. Mehta RS, Saliba RM, Rondon G, et al. Post-transplantation cyclophosphamide versus tacrolimus and methotrexate graft-versus-host disease prophylaxis for HLA-matched donor transplantation. *Transplant Cell Ther*. 2022;28(10):695.e1-695.e10.
32. Carreira AS, Salas MQ, Remberger M, et al. Bloodstream infections and outcomes following allogeneic hematopoietic cell transplantation: a single-center study. *Transplant Cell Ther*. 2022;28(1):50.e1-50.e8.
33. Salas MQ, Chary P, Puerta-Alcalde P, et al. Bacterial bloodstream infections in patients undergoing allogeneic hematopoietic cell transplantation with post-transplantation cyclophosphamide. *Transplant Cell Ther*. 2022;28(12):850.e1-850.e10.
34. Penack O, Marchetti M, Ruutu T, et al. Prophylaxis and management of graft versus host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation. *Lancet Haematol*. 2020;7(2):e157-e167.
35. Soiffer RJ, Kim HT, McGuirk J, et al. Prospective, randomized, double-blind, phase III clinical trial of anti-T-lymphocyte globulin to assess impact on chronic graft-versus-host disease-free survival in patients undergoing HLA-matched unrelated myeloablative hematopoietic cell transplantation. *J Clin Oncol*. 2017;35(36):4003-4011.
36. Walker I, Panzarella T, Couban S, et al; Canadian Blood and Marrow Transplant Group. Pretreatment with anti-thymocyte globulin versus no anti-thymocyte globulin in patients with haematological malignancies undergoing haemopoietic cell transplantation from unrelated donors: a randomised, controlled, open-label, phase 3, multicentre trial. *Lancet Oncol*. 2016;17(2):164-173.
37. Marty FM, Ljungman P, Chemaly RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. *N Engl J Med*. 2017;377(25):2433-2444.
38. Papanicolaou GA, Avery RK, Cordonnier C, et al; AURORA Trial Investigators. Treatment for first cytomegalovirus infection post-hematopoietic cell transplant in the AURORA trial: a multicenter, double-blind, randomized, phase 3 trial comparing maribavir with valganciclovir. *Clin Infect Dis*. 2024;78(3):562-572.
39. Salas MQ, Alfaro-Moya T, Atenafu EG, et al. Outcomes of antithymocyte globulin-post-transplantation cyclophosphamide-cyclosporine-based versus antithymocyte globulin-based prophylaxis for 10/10 HLA-matched unrelated donor allogeneic hematopoietic cell transplantation. *Transplant Cell Ther*. 2024;30(5):536.e1-536.e13.
40. Salas MQ, Atenafu EG, Law AD, et al. Experience using anti-thymocyte globulin with post-transplantation cyclophosphamide for graft-versus-host disease prophylaxis in peripheral blood haploidentical stem cell transplantation. *Transplant Cell Ther*. 2021;27(5):428.e1-428.e9.
41. Law AD, Salas MQ, Lam W, et al. Reduced-intensity conditioning and dual T lymphocyte suppression with antithymocyte globulin and post-transplant cyclophosphamide as graft-versus-host disease prophylaxis in haploidentical hematopoietic stem cell transplants for hematological malignancies. *Biol Blood Marrow Transplant*. 2018;24(11):2259-2264.
42. Yeh J, Whited L, Saliba RM, et al. Cardiac toxicity after matched allogeneic hematopoietic cell transplant in the posttransplant cyclophosphamide era. *Blood Adv*. 2021;5(24):5599-5607.
43. Duléry R, Goulet C, Mannina D, et al. Reduced post-transplant cyclophosphamide doses in haploidentical hematopoietic cell transplantation for elderly patients with hematological malignancies. *Bone Marrow Transplant*. 2023;58(4):386-392.