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Graft-versus-Host Disease Prophylaxis with Post-Transplantation Cyclophosphamide in Chronic Myeloid Leukemia Patients Undergoing Allogeneic Hematopoietic Cell Transplantation from an Unrelated or Mismatched Related Donor: A Comparative Study from the Chronic Malignancies Working Party of the EBMT (CMWP-EBMT)

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A B S T R A C T

Outcomes following allogeneic hematopoietic cell transplantation (allo-HCT) for chronic myeloid leukemia (CML) with post-transplantation cyclophosphamide (PTCy) using an unrelated donor (UD) or a mismatched related donor (MMRD) remain unknown. We report a retrospective comparison of PTCy-based allo-HCT from a UD, non-PTCy allo-HCT from a UD, and PTCy allo-HCT from an MMRD. Inclusion criteria were adult patients with CML undergoing first allo-HCT between 2012 and 2019 from a UD with either PTCy or non-PTCy graft-versus-host disease (GVHD) prophylaxis or from an MMRD using PTCy. The primary endpoint was GVHD-free/relapse-free survival (GRFS). A total of 1341 patients were included (82% in the non-PTCy UD cohort). With a median follow-up of 34.9 months, the 3-year GRFS was 43% in the non-PTCy cohort, 37% in the PTCy-UD cohort, and 39% PTCy-MMRD cohort ($P = .15$). Multivariable analyses revealed no significant differences among the 3 cohorts in terms of overall survival (OS), progression-free survival, RI, and nonrelapse mortality. Factors independently associated with worse OS in the overall cohort were Karnofsky Performance Status <90 (hazard ratio [HR], 1.86; 95% confidence interval [CI], 1.41 to 2.45; $P < .001$), older age (HR, 1.24, 95% CI, 1.11 to 1.38; $P < .001$), and disease stage (compared to chronic phase [CP] 1): blast phase (HR, 2.25; 95% CI, 1.60 to 3.16; $P < .001$), accelerated phase (HR, 1.63; 95% CI, 1.05 to 2.54; $P = .03$), and CP >2 (HR, 1.58; 95% CI, 1.15 to 2.17; $P = .005$). These results suggest that allo-HCT in patients with CML using either a UD or an MMRD with PTCy-based GVHD prophylaxis are feasible transplantation, platforms and that the disease stage at allo-HCT remains a major prognostic factor, highlighting the importance of closely monitoring CML patients and proposing transplantation when indicated when still in CP1.

INTRODUCTION

Tyrosine kinase inhibitors (TKIs) provide the potential of long-term molecular responses in a significant proportion of patients with chronic myeloid leukemia (CML) [1]. However, over time, a significant number may develop resistance or intolerance to a TKI, necessitating additional therapeutic strategies [2]. Overall, selected eligible patients with chronic phase (CP) disease resistant to TKI or with advanced-phase CML (AdP-CML) with an available donor are considered potential candidates for allogeneic hematopoietic cell transplantation (allo-HCT) in several guidelines [3,4]. Allo-HCT provides a T cell-driven graft-versus-leukemia (GVL) effect, which has been reported to be key in controlling disease relapse after transplantation [5]. In this respect, despite the significant nonrelapse mortality (NRM) rates associated with allo-HCT, this approach remains a therapeutic option for CP TKI-resistant CML and AdP-CML [6,7].

The role of donor type in determining post-allo-HCT outcomes in CML has been studied extensively [8–10]. Allo-HCT from matched sibling donors (MSDs) is associated with a lower NRM and a higher OS compared to the use of matched unrelated donors (MUDs) and mismatched unrelated donors (MMUDs) [8]. Unfortunately, <30% of candidates for allo-HSCT have a suitable MSD, and thus a search for a compatible unrelated donor (UD) is recommended. However, allo-HSCT from UDs entails higher risks. HLA mismatch in either the major histocompatibility antigen or the minor histocompatibility antigen setting is associated with higher rates of both graft-versus-host disease (GVHD) and NRM. To reduce GVHD rates, such strategies as T cell depletion (TCD) [11,12] and the use of bone marrow as the graft source [13] have been adopted in this setting. However, these approaches are associated with a greater risk of infections and of relapse, with outcomes of UD allo-HSCT being generally worse overall compared to those of MSD-allo-HSCT.

The advent of post-transplantation cyclophosphamide (PTCy) as GVHD prophylaxis has successfully facilitated the incorporation of mismatched

related donors (MMRDs), predominately haploidentical donors (HDs), into allo-HCT donor selection algorithms. The Baltimore group pioneered the use of PTCy in a nonmyeloablative HD transplantation platform using bone marrow as the graft source, reporting satisfactory results that suggest the viability of such an approach [14]. Subsequently, the use of PTCy as GVHD prophylaxis has been expanded across a wide range of indications and donor types. Indeed, evidence from retrospective studies suggests that in several hematologic malignancies, outcomes after allo-HCT from MMRDs using PTCy are comparable to those after allo-HCT from UDs or MSDs [15–19].

Outcomes of allo-HCT using PTCy in patients diagnosed with CML remain less well established. In the present study, we evaluated the use of PTCy in allo-HCT from UDs and MMRDs in patients with CML and compared the results with those observed after allo-HCT from UDs with non-PTCy GVHD prophylaxis using retrospective data collected in the European Society for Blood and Marrow Transplantation (EBMT) registry.

METHODS

This was a retrospective, multicenter, registry-based analysis approved by the Chronic Malignancies Working Party of the EBMT. The EBMT is a nonprofit scientific society representing more than 600 transplant centers located mainly in Europe. Data are entered, managed, and maintained in a central database with internet access; each EBMT center is represented in this database. EBMT centers commit to obtain informed consent according to the local regulations applicable at the time for reporting pseudonymized data to the EBMT. Patient selection was performed by identifying CML patients undergoing a first allo-HCT between 2012 and 2019 from a UD using PTCy as GVHD prophylaxis (PTCy UD), allo-HCT from UD using a non-PTCy GVHD prophylaxis (non-PTCy UD) and allo-HCT from MMRD with PTCy as GVHD prophylaxis (PTCy MMRD). All patients were age $\geq$18 years at allo-HCT, and all CML disease types were included. Patients undergoing allo-HCT from an MSD or using cord blood as the graft source were excluded. Response was assessed according to the European LeukemiaNet 2009 and 2013 guidelines [20,21]. Disease diagnosis and disease phase criteria were defined according to the World Health Organization criteria [22,23]. Primary graft failure was defined as failing to reach an absolute neutrophil count $>.5 \times 10^9$/L within the first 28 days after stem cell infusion or documentation of autologous reconstitution by chimerism analysis in the absence of relapse. Secondary graft failure was defined as a decline in hematopoietic function (possibly involving hemoglobin and/or platelets and/or neutrophils) necessitating blood product or growth factor support, after having met the standard definition of hematopoietic (neutrophils and platelets) recovery.

Outcomes

The primary endpoint was GVHD-free/relapse-free survival (GRFS), defined as the time from the date of allo-HCT to the first date of the following events: acute GVHD (aGVHD) grade III or IV, extensive chronic GVHD (cGVHD), relapse, or death, whichever occurred first. Secondary endpoints were overall survival (OS), progression free-survival (PFS), cumulative relapse incidence (RI), NRM, and cumulative incidence of grade II-IV aGVHD and cGVHD (limited and extensive). Of note, different criteria were used to assess GVHD within the study. aGVHD was graded according to 2 different criteria depending on the year of GVHD diagnosis [24,25], and cGVHD was assessed according to 2 different National Institutes of Health criteria [26,27].

Statistical Analysis

Clinical, demographic, and transplantation-related characteristics at baseline were tabulated and compared in the PTCy UD, non-PTCy UD, and PTCy MMRD groups using the chi-square test for categorical variables and the Kruskal-Wallis test for continuous data. Baseline was defined as the day of allo-HCT. The median follow-up after baseline and 95% CIs were calculated using the reverse Kaplan-Meier method. The time to neutrophil engraftment (first day of 3 consecutive days with a count $>.5 \times 10^9$/L) and the time to platelet engraftment (first of 3 consecutive days with a count $>20 \times 10^9$/L) were analyzed using the cumulative incidence estimator (with death as a competing event), and the Gray test was used to compare differences among the groups. The primary endpoint (GRFS) and secondary endpoints (OS and PFS) were analyzed using the Kaplan-Meier estimator, and the log-rank test was used to assess differences between groups. NRM together with RI, aGVHD together with death before aGVHD, and cGVHD together with death before cGVHD were analyzed in a competing risk framework, and the Gray test was used to compare differences between groups. Multivariable Cox proportional hazards models were fitted

to assess the associations between the 3 donor/-prophylaxis groups (non-PTCy UD, PTCy UD, PTCy MMRD) and outcomes (OS, PFS, RI, and NRM), adjusted for potential confounders. Cause-specific hazard models were used for RI, NRM, aGVHD, and cGVHD.

All multivariable analyses (MVAs) were performed based on complete cases. As a sensitivity analysis for OS, the substantive model compatible fully conditional specification imputation of covariates approach was used to impute multiple values (50 times) for all covariates included in the analysis of OS that had missing values. The resulting 50 datasets were analyzed separately, and results were combined using Rubin's rules [28]. For aGVHD/death with aGVHD, outcomes were artificially censored at 100 days after allo-HCT; all other outcomes were artificially censored at 36 months after allo-HCT.

The following variables were considered as potential confounders: patient age at allo-HCT, donor age, patient sex, graft source, number of different types of TKI before allo-HCT (imatinib, dasatinib, nilotinib, bosutinib, ponatinib, and asciminib), type of conditioning (myeloablative conditioning [MAC] versus reduced-intensity conditioning), type of GVHD prophylaxis, TCD, total body irradiation, disease status (CP1 versus others) at allo-HCT, Karnofsky Performance Status (KPS), Hematopoietic Cell Transplantation Specific-Comorbidity Index (HCT-CI), donor/recipient cytomegalovirus serostatus (-/-, other), year of allo-HCT, and the time from diagnosis to allo-HCT. All statistical tests were 2-sided, and significance was determined at $P \leq .05$. All analyses were performed in R version 4.2.2;28 using the survival, cmprsk, prodlim, and smcfcs packages.

RESULTS

A total of 1341 CML patients treated in 257 EBMT centers were selected from the registry. A total of 1094 patients (82%) underwent non-PTCy UD, 113 patients (8%) underwent PTCy UD allo-HCT, and 134 patients (10%) underwent PTCy MMRD allo-HCT. Table 1 displays patient- and transplantation-specific characteristics across the 3 donor/GVHD prophylaxis cohorts. The median age at allo-HCT in the entire population was 47 years (interquartile range [IQR], 37 to 56 years). The majority of the non-PTCy UD cohort received calcineurin inhibitor-based GVHD prophylaxis (88%) (Table 2). TCD was used in 83% of the non-PTCy UD patients, 19% of the PTCy UD patients, and 9% of the PTCy MMRD patients. Supplementary Table S1 provides details on TCD. In the 990 patients with available data on the type of TKI treatment, 650 (65.8%) were treated with imatinib at any point before allo-HCT, 611 (61.8%) received dasatinib, 490 patients (49.6%) received nilotinib, 107 (10.8%) received bosutinib, 278 (28.1%) received ponatinib, and 4 (.4%) received asciminib. Previous treatment with ponatinib was recorded in 222 patients (27.4%) in the non-PTCy UD group, 21 patients (24.4%) in the PTCy UD group, and 35 patients (37.6%) in the PTCy MMRD group. The median duration of follow-up after allo-HCT was 34.9 months (IQR, 13.2 to 61.2 months).

Engraftment Analysis

The median time to neutrophil engraftment ($>.5 \times 10^9$/L) was 16 days (IQR, 13 to 20 days) for the non-PTCy UD allo-HCT group, 20 days (IQR, 17 to 23 days) for the PTCy UD allo-HCT group, and 19 days (IQR, 16 to 24 days) for the PTCy MMRD allo-HCT group. The median time to platelet engraftment ($>20 \times 10^9$/L) in the 3 groups was 15 days (IQR, 12 to 21 days), 20 days (IQR, 14 to 32 days), and 27 (days IQR, 19 to 37 days), respectively.

Primary graft failure (PGF) occurred in 25 patients (1.9%), including 14 patients (1.3 %) in the non-PTCy UD group, 3 patients (2.8%) in the PTCy UD group, and 8 patients (6.3%) in the PTCy MMRD group ($P < .001$). The 3-year cumulative incidence of secondary graft failure in the 3 groups was 3% (95% CI, 2% to 4%), 1% (95% CI, 0 to 3%), and 10% (95% CI, 4% to 15%), respectively ($P = .002$, Gray test).

OS

With a median follow up of 35 months (IQR, 31 to 37 months), the 3-year OS in all included patients was 63% (95% CI, 60% to 66%). In univariable analysis (Supplementary Table S2, Figure 1), OS was not significantly different according to donor/GVHD prophylaxis group (P = .51) and was significantly better in more recent transplantations, in patients with KPS $\geq$90, in low-risk HCT-CI patients (Figure 2A), in patients in CP1 disease stage (Figure 2B), and in patients age $<$45 years at allo-HCT.

The OS MVA, which included 902 patients (68%) with complete data, showed no evidence that the risk of death was different in the 3 donor/-prophylaxis groups (HR for non-PTCy UD versus PTCy UD, .81 [95% CI, .53 to 1.25]; for PTCy MMRD versus PTCy UD, 1.10 [95% CI, .62 to 1.93]; overall $P = .30$) (Table 3). Furthermore, older age at allo-

Table 1
Patient, Disease, and Transplantation Characteristics

Characteristic	Total	Non-PTCy UD Group	PTCy UD Group	PTCy MMRD Group	*P* Value
No. of patients (%)	1341	1094 (81.6)	113 (8.4)	134 (10.0)	
Age at allo-HCT, yr, median (IQR)	47.5 (36.6-56.2)	48 (37.6-56.6)	43.5 (33.2-53)	45.7 (33.9-53.2)	.004
Male sex, n (%)	835 (62.3)	680 (62.2)	73 (64.6)	82 (61.2)	.85
Year of allo-HCT, median (IQR)	2015 (2013-2017)	2015 (2013-2017)	2017 (2015-2018)	2016 (2014-2018)	<.001
Disease stage at allo-HCT, n (%)					
CP1	584 (43.5)	506 (46.3)	37 (32.7)	41 (30.6)	<.001
CP2	283 (21.1)	223 (20.4)	29 (25.7)	31 (23.1)	
≥CP3	53 (4.0)	41 (3.7)	7 (6.2)	5 (3.7)	
CP not specified	45 (3.4)	42 (3.8)	2 (1.8)	1 (.7)	
Accelerated phase	145 (10.8)	104 (9.5)	21 (18.6)	20 (14.9)	
Blast crisis	231 (17.2)	178 (16.3)	17 (15.0)	36 (26.9)	
Conditioning (N = 1321; 99%), n (%)					
MAC	813 (61.5)	667 (61.9)	58 (52.3)	88 (66.2)	.07
RIC	508 (38.5)	410 (38.1)	53 (47.7)	45 (33.8)	
TBI, n (%)					
No	1008 (75.6)	807 (74.2)	95 (84.8)	106 (79.1)	.03
Yes	325 (24.4)	280 (25.8)	17 (15.2)	28 (20.9)	
Donor type, n (%)					
MMRD	134 (10.0)			134 (100)	<.001
MUD	728 (54.3)	667 (61.0)	61 (54.0)		
MMUD	242 (18.0)	207 (18.9)	35 (31.0)		
UD mismatches unknown	237 (17.7)	220 (20.1)	17 (15.0)		
Previous TKI (N = 990; 74%), n (%)					
0	50 (5.1)	42 (5.2)	2 (2.3%	6 (6.5)	.59
1-2	556 (56.2)	450 (55.5)	54 (62.8)	63 (47.0)	
≥3	384 (38.8)	319 (39.3)	30 (34.9)	23 (17.2)	
Last pre-allo-HCT treatment (N = 990; 74%), n (%)					
TKI + chemotherapy	312 (31.6)	255 (31.5)	24 (27.9)	33 (35.5)	.34
TKI	597 (60.4)	491 (60.7)	57 (66.3)	49 (52.7)	
Chemotherapy	79 (8.0)	63 (7.8)	5 (5.8)	11 (11.8)	
KPS at allo-HCT (N = 1264, 94%), n (%)					
≥90	993 (78.6)	819 (79.4)	80 (74.8)	94 (75.2)	.34
<90	271 (21.4)	213 (20.6)	27 (25.2)	31 (24.8)	
HCT-CI risk (N = 970; 72%), n (%)					
Low risk (0)	586 (60.6)	466 (59.4)	60 (69.8)	60 (62.5)	.32
Intermediate risk (1-2)	231 (23.9)	196 (25.0)	13 (15.1)	22 (22.9)	
High risk (≥3)	150 (15.5)	123 (15.7)	13 (15.1)	14 (14.6)	
Recipient/donor CMV serostatus (N = 1296; 97%), n (%)					
-/-	372 (28.7)	339 (32.0)	17 (16.0)	16 (12.1)	<.001
Other	924 (81.3)	719 (68.0)	89 (84.0)	116 (87.9)	
Graft source, n (%)					
Bone marrow	200 (14.9)	116 (10.6)	18 (15.9)	66 (49.3)	<.001
Peripheral blood	1141 (85.1)	978 (89.4)	95 (84.1)	68 (50.7)	

P values were obtained using the chi-square test for categorical variables and the Kruskal-Wallis test for continuous data.
TBI indicates total body irradiation; RIC, reduced-intensity conditioning; CMV, cytomegalovirus.

Table 2
Distribution of GVHD Prophylaxis across the 3 Donor/Prophylaxis Groups

Parameter	Group	Total, n (%)	Non-PTCy UD Group, n (%)	PTCy UD Group, n (%)	PTCy MMRD Group, n (%)	*P* Value
Total		1341 (100)	1094 (100)	113 (100)	134 (100)	
GVHD prophylaxis*	PTCy	247 (18.4)	0 (0)	113 (100)	134 (100)	<.001
	CsA	1087 (81.1)	959 (87.7)	30 (26.5)	98 (73.1)	<.001
	Tacrolimus	225 (16.8)	133 (12.2)	55 (48.7)	37 (27.6)	<.001
	MMF	482 (35.9)	294 (26.9)	67 (59.3)	121 (90.3)	<.001
	Sirolimus	32 (2.4)	23 (2.1)	4 (3.5)	5 (3.7)	.36
	MTX	651 (48.5)	635 (58.0)	12 (10.6)	4 (3.0)	<.001
TCD (N = 1326; 99%)	No	397 (29.9)	187 (17.3)	92 (81.4)	118 (90.8)	<.001
	Yes	929 (70.1)	896 (82.7)	21 (18.6)	12 (9.2)	

CsA indicates cyclosporine; MMF, mycophenolate mofetil; MTX, methotrexate.
Percentages do not sum to 100%, as GVHD prophylaxis drugs are not mutually exclusive. *P* values were obtained using the chi-square test for categorical variables.

HCT was associated with an increased risk of death (HR, 1.24 per 10 years older; 95% CI, 1.11 to 1.38; $P < .001$), as was a lower KPS (HR for <90 versus ≥90, 2.04; 95% CI, 1.64 to 2.45; $P < .001$), and more advanced disease stage at allo-HCT (HR for CP ≥2 versus CP1, 1.58 [95% CI, 1.15 to 2.17; $P = .005$]; for AP-CML versus CP1, 1.63 [95% CI, 1.05 to 2.54; $P < .03$]; for BP versus CP1, 2.25 [95% CI, 1.60 to 3.16; $P < .001$]). There was no evidence that the association between disease stage and OS differed among the 3 GVHD prophylaxis/donor groups (interaction disease stage × GVHD prophylaxis/donor group, $P = .19$).

By way of sensitivity analysis, the OS MVA also was performed using multiple imputations of the missing data (Supplementary Table S3). As in the complete case analysis, there was no significant difference among the 3 donor/GVHD prophylaxis groups (HR for non-PTCy UD versus PTCy UD, .84 [95% CI, .60 to 1.19]; for PTCy MMRD versus PTCy UD, 1.00 [95% CI, .63 to 1.57]). The risk of death was lower in patients who underwent allo-HCT in more recent years (HR per year later, .95; 95% CI, .90 to 1.00; $P = .03$). Estimates of other variables were close to those obtained in the complete-case analysis.

PFS

The 3-year PFS was 52% (95% CI, 49% to 55%). In univariable analyses, PFS was better in the non-PTCy UD group compared to the PTCy UD and PTCy MMRD groups (P = .05, log-rank test) (Supplementary Table S2, Figure 1). PFS also was significantly higher in patients age <45 years at allo-HCT, in patients in disease stage CP1 at allo-HCT, and in patients with KPS ≥90. PFS was significantly lower in patients with a high-risk HCT-CI score.

The PFS MVA did not show a significant association between PFS and any of the 3 donor/GVHD prophylaxis groups (HR for non-PTCy UD versus PTCy UD, .77 [95% CI, .53 to 1.11]; for PTCy MMRD versus PTCy UD, 1.06 [95% CI, .66 to 1.71] ($P = .11$; Table 3). Furthermore, older age at allo-HCT, lower KPS, more advanced disease stage, and more comorbidities at allo-HCT were independently associated with lower PFS.

RI

The 3-year RI was 28% (95% CI, 25% to 31%). In univariable analyses, RI was significantly lower in the non-PTCy UD cohort (26%; 95% CI, 23% to 29%) compared to the PTCy UD (35%; 95% CI, 25% to 44%) and PTCy MMRD (34%; 95% CI, 25% to 43%) cohorts ($P = .03$, Gray test) (Supplementary Table S2, Figure 1). Furthermore, RI was significantly better in patients with an ≥18-month interval from diagnosis to allo-HCT compared to <18 months, in patients undergoing allo-HCT in CP1, in patients with KPS ≥90, and in low-risk HCT-CI patients.

The MVA for relapse did not show any significant association between the risk of relapse and the 3 donor/GVHD prophylaxis groups (HR for non-PTCy UD versus PTCy UD, .74 [95% CI, .47 to 1.16]; for PTCy MMRD versus PTCy UD, .90 [95% CI, .50 to 1.64]; $P = .33$) (Table 3). Furthermore, KPS ≥90 (HR, 2.04; 95% CI, 1.52 to 2.73; $P < .001$), BP versus CP1 (HR, 2.13; 95% CI, 1.49 to 3.06; $P < .001$) and CP≥2 versus CP1 (HR, 1.55; 95% CI, 1.11 to 2.16; $P = .002$) were associated with an elevated risk of relapse.

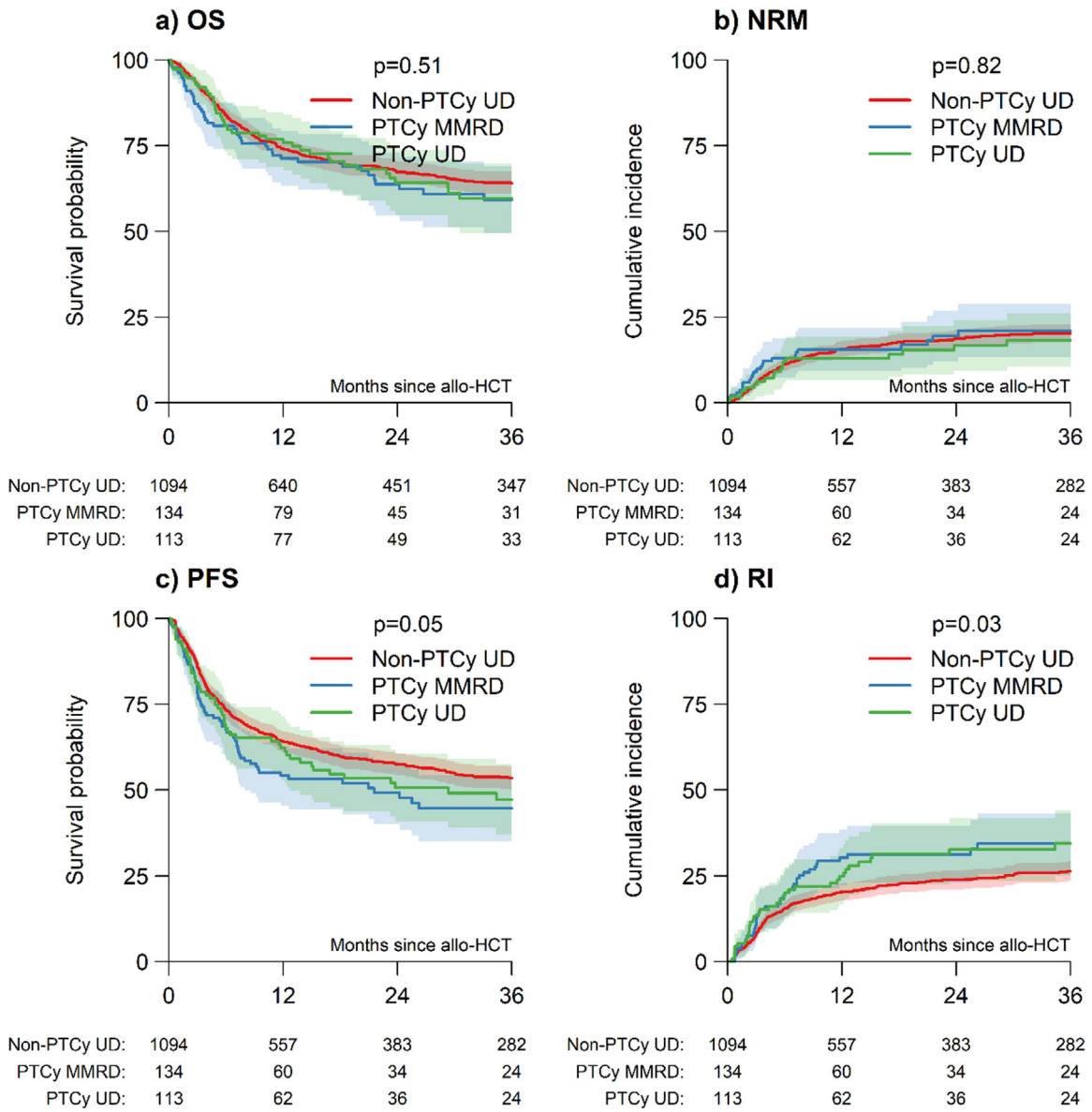

Figure 1. Outcomes after allo-HCT according to the type of GVHD prophylaxis and donor. (A) Probability of OS. (B) Cumulative incidence of NRM. (C) Probability of PFS/RFS. (D) Cumulative RI. Numbers below the graphs show the number of patients at risk. Shaded areas in the graph represent 95% CIs.

NRM

The 3-year cumulative incidence of NRM was 20% (95% CI, 18% to 22%). The univariable analyses shown in Supplementary Table S2 show that the cumulative incidence of NRM was not significantly different across the 3 donor/GVHD prophylaxis groups (P = .82, Gray test) (Figure 1). NRM was significantly higher in patients age ≥45 years at allo-HCT, in patients with a ≥18-month interval between CML diagnosis and allo-HCT, and in patients with a high HCT-CI risk score compared to those with a low or intermediate score.

The MVA for NRM did not identify any significant differences among the 3 donor/GVHD prophylaxis groups (HR for non-PTCy UD versus PTCy UD, .83 [95% CI, .43 to 1.58]; for PTCy MMRD versus PTCy UD, 1.37 [95% CI, .62 to 3.03]; P = .22). There was an association between older recipient age at allo-HCT and increased risk of NRM (HR per 10-year increase, 1.26; 95% CI, 1.08 to 1.47; P = .004) and between more comorbidities and increased risk of NRM (Table 3).

GVHD and GRFS Analysis

We did not observe any significant differences in the GRFS curve (P = .16, log-rank test). The 1-year GRFS was 53% (95% CI, 50% to 57%) in the non-PTCy UD group, 52% (95 CI, 42% to 62%) in the PTCy UD group, and 45% (95% CI, 36% to 54%) in the PTCy MMRD group. The 3-year GRFS in the 3

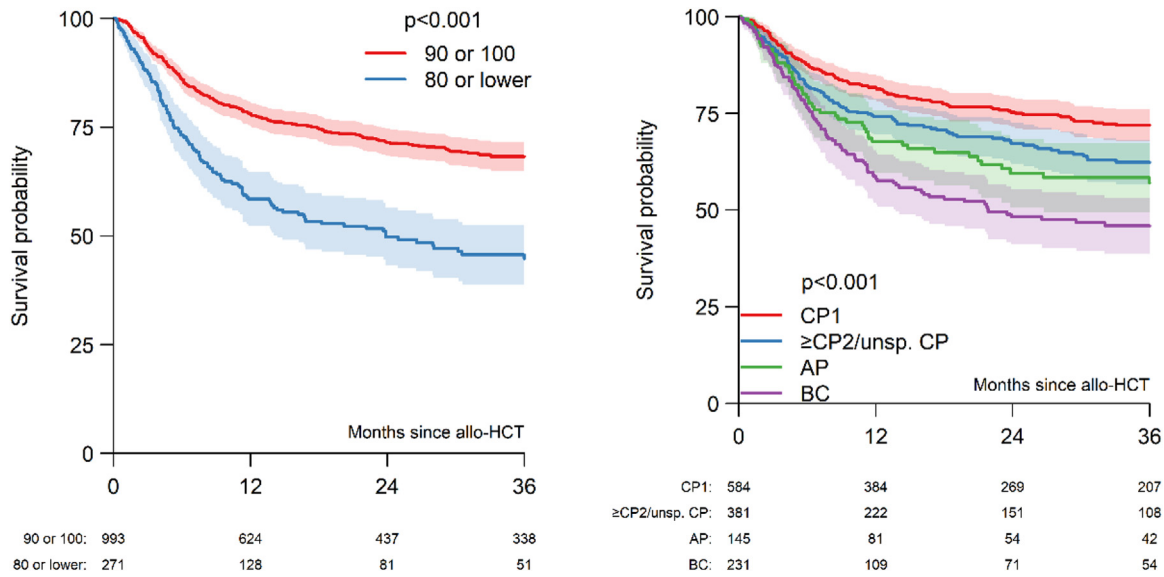

Figure 2. Probability of OS after allo-HCT according to KPS (A) and pre-allo-HCT disease stage (B). Numbers below the graphs indicate the number of patients at risk. Shaded areas in the graph represent 95% CIs. Tx, transplantation.

groups was 42% (95% CI, 39% to 45%), 37% (95% CI, 27% to 48%), and 37% (95 CI, 27% to 46.9%), respectively (Figure 3A).

The 100-day cumulative incidence of grade II-IV aGVHD in all included patients was 25% (95% CI, 23% to 28%). The univariable analyses described in Supplementary Table S4 and Figure 3B show no statistically significant differences in the cumulative incidence of aGVHD according to type of donor ($P = .03$, Gray test).

The 1-year and 3-year cumulative incidence of cGVHD was 14% (95% CI, 12% to 16%) and 20% (95% CI, 18% to 23%), respectively. There were no significant differences in the cumulative incidence of cGVHD according to donor/prophylaxis group ($P = .55$, Gray test) (Figure 3C).

The MVA of aGVHD showed no evidence of an association between donor/GVHD prophylaxis group ($P = .39$) and the risk of aGVHD (HR for non-PTCy UD versus PTCy UD, 1.14 [95% CI, .72 to 1.82]; for PTCy MMRD versus PTCy UD, .82 [95% CI, .43 to 1.56]) (Supplementary Table S5). There was no evidence that the risk of cGVHD differed among the 3 donor/GVHD prophylaxis groups ($P = .70$).

Response and Treatment after Allo-HCT

Among 1233 evaluable patients, 83.4% (95% CI, 80.9% to 85.7%) of non-PTCy UD patients, 85.5% (95% CI, 77.5% to 91.5%) of PTCy UD patients, and 78.0% (95% CI, 69.7% to 85.0%) of PTCy MMRD patients were in hematologic CR at day +100. Available data on the depth of response according to type of donor and GVHD prophylaxis are provided in Supplementary Table S6.

Data on therapeutic approaches after allo-HCT were available for only 399 patients (29.7%); 88 of these patients received at least 1 donor lymphocyte infusion. Additional data on other possible treatments after allo-HCT were unavailable.

DISCUSSION

Talen together, our data suggest that GRFS was comparable in CML patients undergoing allo-HCT from UD irrespective of the GVHD prophylaxis used. These results show that in this cohort, PTCy-based GVHD prophylaxis provides similar outcomes as those using non-PTCy GVHD prophylaxis, based on calcineurin inhibitor use and TCD in most patients. However, we cannot rule out the clinically meaningful differences in outcomes between cohorts, given the limited number of PTCy patients and the unbalanced distribution of GVHD prophylaxis including TCD between groups. Additionally, disease status at time of allo-HCT, patient age, KPS, and HCT-CI were identified as prognostic factors.

Interestingly, univariable analysis showed a higher PFS and a lower RI in the non-PTCy compared to the PTCy cohorts, whereas these differences were not significant in MVA. This might be explained by the higher proportion of patients with characteristics associated with better outcome (less Adv-CML and less comorbidity) in the non-PTCy UD cohort compared to the PTCy cohorts. The effect of disease status on PFS is well

Table 3
HRs for OS and PFS, Cause-Specific HRs for Relapse and NRM and 95% CIs Obtained with Multivariable Cox Proportional Hazard Models

	OS		PFS		RI		NRM	
Variable	HR (95% CI)	(Overall*) *P* Value	HR (95% CI)	(Overall*) *P* Value	HR (95% CI)	(Overall*) *P* Value	HR (95% CI)	(Overall*) *P* Value
Donor/GVHD prophylaxis group		(.30)		(.11)		(.33)		(.22)
UD/PTCy	1.00		1.00		1.00		1.00	
UD/no PTCy	.81 (.53-1.25)	.34	.77 (.53-1.11)	.16	.74 (.47-1.16)	.18	.83 (.43-1.58)	.57
MMRD/PTCy	1.10 (.62-1.93)	.75	1.06 (.66-1.71)	.81	.90 (.50-1.64)	.74	1.37 (.62-3.03)	.44
Age at allo-HCT (per 10-yr increase)	1.24 (1.11-1.38)	.0002	1.15 (1.05-1.26)	.004	1.09 (.97-1.22)	.16	1.26 (1.08-1.47)	.004
Sex								
Male	1.00		1.00		1.00		1.00	
Female	.90 (.69-1.17)	.43	.94 (.76-1.17)	.57	.88 (.67-1.16)	.36	1.04 (.73-1.47)	.82
Recipient/donor CMV serostatus								
-/-	1.00		1.00		1.00		1.00	
Other	1.05 (.78-1.40)	.76	1.01 (.79-1.28)	.95	.94 (.70-1.26)	.66	1.13 (.76-1.67)	.55
KPS at allo-HCT								
≥90	1.00		1.00		1.00		1.00	
<90	1.86 (1.41-2.45)	<.0001	1.69 (1.33-2.14)	<.0001	2.04 (1.52-2.73)	<.0001	1.18 (.77-1.80)	.44
Stage at allo-HCT		(<.0001)		(.0008)		(.0006)		(.44)
CP1	1.00		1.00		1.00		1.00	
AP	1.63 (1.05-2.54)	.03	1.45 (1.00-2.11)	.05	1.41 (.86-2.32)	.17	1.50 (.85-2.67)	.17
BP	2.25 (1.60-3.16)	<.0001	1.77 (1.32-2.37)	.0001	2.13 (1.49-3.06)	<.0001	1.25 (.75-2.06)	.39
≥CP2/unspecified CP	1.58 (1.15-2.17)	.005	1.45 (1.12-1.88)	.005	1.55 (1.11-2.16)	.01	1.31 (.87-1.97)	.20
Stem cell source								
Bone marrow	1.00		1.00		1.00		1.00	
Peripheral blood	1.37 (.88-2.11)	.16	1.12 (.79-1.58)	.51	.95 (.62-1.44)	.80	1.52 (.82-2.81)	.18
Conditioning intensity								
MAC	1.00		1.00		1.00		1.00	
RIC	.88 (.67-1.16)	.36	.99 (.78-1.25)	.92	1.07 (.79-1.44)	.67	.87 (.60-1.28)	.49
HCT-CI risk score		(.01)		(.0004)		(.04)		(.0003)
Low	1.00		1.00		1.00		1.00	
Intermediate	1.35 (1.00-1.83)	.05	1.48 (1.15-1.90)	.002	1.49 (1.09-2.03)	.01	1.46 (.95-2.24)	.08
High	1.60 (1.15-2.22)	.006	1.64 (1.24-2.16)	.0006	1.27 (.87-1.85)	.22	2.37 (1.55-3.61)	<.0001
Year of allo-HCT (per year later)	.98 (.92-1.04)	.56	.98 (.93-1.03)	.47	1.00 (.94-1.07)	1.00	.95 (.88-1.03)	.22

AP, accelerated phase; CP chronic phase; BP: blast phase.
* Overall *P* values were obtained with the likelihood ratio test.

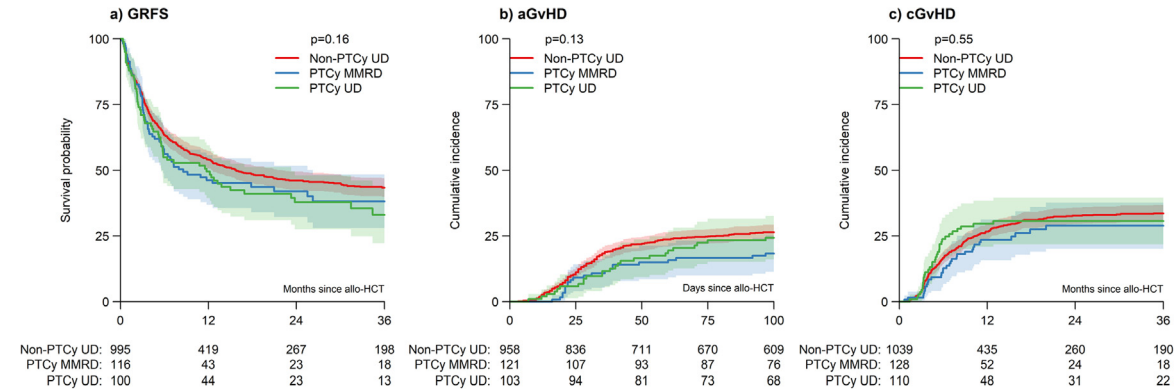

Figure 3. Outcomes after allo-HCT according to the type of donor and GVHD prophylaxis. (A) Probability of GRFS. (B) Cumulative incidence of aGVHD. (C) Cumulative incidence of cGVHD. Numbers below the graphs show the number of patients at risk. Shaded areas in the graph represent 95% CIs.

established [29], and as in that study, we also found that CP1 remains a major prognostic factor. Compared to AdP-CML, CP1-CML is associated less frequently with additional chromosomal abnormalities, kinase domain *BCR::ABL1* point mutations, or somatic cancer gene mutations, which have been linked to worse outcomes [30–32].

On the other hand, the use of a UD has been linked to a higher NRM and lower OS compared to MSDs in CML allo-HCT [8,9] This has been attributed mainly to higher rates of GVHD and the complications associated with GVHD. Comparisons of PTCy MMRD with non-PTCy UD in different hematologic diagnoses have shown contrasting results regarding NRM [33,34]. In our study, NRM estimates were not significantly different based on the type of donor and GVHD prophylaxis.

Moreover, KPS was identified in MVA as a strong prognostic factor for RI, PFS, and OS. Our findings further corroborate previously reported data in CML patients [35]. In this respect, we note that the patient age distribution was unbalanced among the cohorts, with the PTCy UD cohort including younger patients compared to the others. Of note, this study included mainly MAC allo-HCT, possibly because AdP-CML patents were included. Interestingly, reduced-intensity conditioning provided similar survival as MAC in MVA, in line with previously reported data [36].

Finally, we observed that the OS according to disease stage was significantly higher in CP1 patients compared to AdP-CML patients. In contrast, long-term outcomes of newly diagnosed accelerated phase CML (AP-CML) patients were similar to those in CP-CML patients in some series [37] and in this respect, considering AP-CML patients as CP-CML patients has been suggested [38]. Our cohort includes AP-CML patients undergoing allo-HCT, which might not be representative of all newly diagnosed AP-CML patients and hence the different prognosis.

Our retrospective, registry-based study is somewhat limited by incomplete data in some areas. We acknowledge that data on additional chromosomal abnormalities, *BCR::ABL1* kinase domain, and cancer gene mutations would have been relevant to better understand the outcomes, as these are key prognostic variables in current CML practice [1]. Furthermore, the MVA was hampered by missing data, primarily on HCT-CI. However, the analysis of OS in which missing values were replaced by multiple imputed values provided similar results, providing reassurance that results based on complete cases can be trusted. Moreover, we did not have enough available data on post-transplantation infection, which has an impact on NRM. It is interesting that there were more patients undergoing allo-HCT using bone marrow in the MMRD cohort compared to the UD cohorts, and this cohort was associated with a higher rate of graft failure. Additionally, we cannot fully understand the outcomes of the non-PTCy cohort, as this included TCD as GVHD prophylaxis in most patients. Finally, missing data on the use of TKI or DLI after transplantation precluded us from reaching more solid conclusions on disease relapse or PFS. Generally, TKI after allo-HCT has been reported to be safe, but its role in maintenance remains unclear, particularly in CP1 transplantation recipients.

According to these results, PTCy UD is a feasible transplantation platform in CML patients lacking an MSD and should be taken into consideration by physicians for patient counseling and clinical decision making. Whether or not to use PTCy as GVHD prophylaxis for CML patients undergoing allo-HCT in the UD setting remains unclear. Our results also show that PTCy is a feasible transplantation

platform in the MMRD setting. Additionally, pre-transplantation disease stage remains a major prognostic factor, with better outcomes in CP1 patients compared to AdP-CML patients, emphasizing the need to closely monitor CML patients and, if transplantation is needed, to propose it, if possible, when patients are still in CP1.

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Authorship statement: Concept and design were undertaken by Y.C, G.O., and L.G. and approved by all authors. Data analysis was performed by L.G. Collection and assembly of data were performed by all authors. All authors contributed to manuscript writing and final approval.

Data availability statement: Data are available on request from the Chronic Malignancies Working Party.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2023.09.019.

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