Received: 13 January 2024 | Accepted: 25 March 2024

DOI: 10.1111/bjh.19448

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

ORIGINAL PAPER

Transplantation

Mismatched related donor allogeneic haematopoietic cell transplantation compared to other donor types for Ph+ chronic myeloid leukaemia: A retrospective analysis from the Chronic Malignancies Working Party of the EBMT

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Summary

Allogeneic haematopoietic cell transplantation (allo-HCT) remains an option for tyrosine kinase inhibitor-resistant chronic myeloid leukaemia (CML) in first chronic phase (CP1) and high-risk patients with advanced disease phases. In this European Society for Blood and Marrow Transplantation (EBMT) registry-based study of 1686 CML patients undergoing first allo-HCT between 2012 and 2019, outcomes were evaluated according to donor type, particularly focusing on mismatched related donors (MMRDs). Median age at allo-HCT was 46 years (IQR 36–55). Disease status was CP1 in 43%, second CP (CP2) or later in 27%, accelerated phase in 12% and blast crisis in 18%. Donor type was matched related (MRD) in 39.2%, MMRD in 8.1%, matched unrelated (MUD) in 40.2%, and mismatched unrelated (MMUD) in 12.6%. In 4 years, overall survival (OS) for MRD, MMRD, MUD and MMUD was 61%, 56%, 63% and 59% ($p = 0.21$); relapse-free survival (RFS) was 48%, 42%, 52% and 46% ($p = 0.03$); cumulative incidence of relapse (CIR) was 33%, 37%, 27% and 30% ($p = 0.07$); non-relapse mortality (NRM) was 19%, 21%, 21% and 24% ($p = 0.21$); and graft-versus-host disease (GvHD)-free/relapse-free survival (GRFS) was 16%, 18%, 22% and 15% ($p = 0.05$) respectively. On multivariate analysis, MMRD use associated with longer engraftment times and higher risk of graft failure compared to MRD or MUD. There was no statistical evidence that MMRD use associated with different OS, RFS and incidence of GvHD compared to other donor types.

[Correction added on 12 August 2025, after first online publication: The copyright line was changed.]

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KEYWORDS
allogeneic haematopoietic cell transplant, chronic myeloid leukaemia, cyclophosphamide, haploidentical donor, mismatched related donor, post-transplant, TKI resistance

INTRODUCTION

Targeted therapy with tyrosine kinase inhibitors (TKIs) has revolutionized the treatment paradigm of 'Philadelphia-positive' chronic myeloid leukaemia (Ph+ CML), representing standard of care and rapidly superseding allogeneic haematopoietic cell transplantation (allo-HCT), with a proportion of patients gaining treatment-free remission.[1] Nonetheless, more than two decades after the introduction of TKIs, a proportion of 'transplant-eligible' patients with Ph+ CML still require allo-HCT, with drug resistance being the most common indication in first chronic phase (CP1).[2] Indeed, according to a population-based analysis from the Swedish CML Registry, among CP1 patients undergoing allo-HCT, TKI resistance was the indication for transplant in 62.5% of cases.[3] Here, the cumulative probability of undergoing allo-HCT within 5 years following the diagnosis of Ph+ CML in CP with <65 years of age was about 10%.[3] Allo-HCT is currently indicated for most transplant-eligible patients with advanced disease phases. Indeed, in blast crisis (BC), general recommendation is treatment with second- or third-generation TKIs, plus possible induction chemotherapy. For patients diagnosed in accelerated phase (AP), allo-HCT following TKI treatment represents a clinical option on an individualized basis, depending on patient age, performance status and disease characteristics including karyotype and molecular genetics. For those transplant-eligible patients progressing from CP to AP during TKI therapy, allo-HCT should ideally be rapidly considered after obtaining as optimal a response as possible.[4]

Reported survival outcomes in patients with Ph+ CML transplanted in CP1 from a matched related donor (MRD) or matched unrelated donor (MUD) are acceptable but little focused published data exist concerning allo-SCT utilizing mismatched related donors (MMRDs), in CML in CP1.[5,6] Of note, one single-centre, retrospective study suggested that allo-HCT using a MMRD appears to be not inferior to that from a MRD for patients with Ph+ CML in BC or those patients in CP2 from a previous BC, with similar 3-year overall survival (OS) and relapse-free survival (RFS).[7] Moreover, we have recently published on the outcomes between URD using post-transplant cyclophosphamide (PTCy) or non-PTCy graft-versus-host disease (GvHD) prophylaxis and MMRD allo-HCT using PTCy.[8] Given the well-documented sensitivity of the disease to the immunological graft-versus-leukaemia (GvL) effect, transplants from MMRD may be beneficial in high-risk Ph+ CML patients in CP compared to other donor types. In this retrospective registry-based study, we compared the outcomes of patients with Ph+ CML undergoing allo-HCT according to donor type, that is, MRD versus MUD versus MMRD versus mismatched unrelated donor (MMUD).

METHODS

This study was conducted on behalf of the Chronic Malignancies Working Party (CMWP) of the EBMT. The EBMT is a non-profit scientific society representing more than 600 transplant centres mainly in Europe. EBMT centres commit to obtain informed consent according to the local regulations applicable at the time in order to report pseudonymized data stored in a central database. We selected patients from this database who had underwent first allo-HCT for the treatment of Ph+ CML between 2012 and 2019 from a MRD, MMRD, MUD or MMUD. Patients who received post-transplantation cyclophosphamide (PTCy)-based GvHD prophylaxis for transplant from a donor type other than MMRD were excluded as were those in whom umbilical cord blood was used as a graft source. RIC or myeloablative conditioining (MAC) were defined as per standard EBMT criteria.[9]

Outcomes

The primary end-point was OS. Secondary end-points were RFS, cumulative incidence of relapse incidence (CIR), non-relapse mortality (NRM), cumulative incidence of grade II–IV acute and chronic GvHD (cGvHD; limited and extensive) and GvHD relapse-free survival (GRFS). OS was defined as the time from allo-HCT to death from any cause. RFS was defined as the time between allo-HCT and relapse/progression of disease or death, whichever occurred first. NRM was defined as death before relapse/progression of disease and GRFS was defined as the time from the date of allo-HCT to the first date of the following events: acute GvHD (aGvHD) grade II, III or IV; limited or extensive cGvHD; and relapse or death, whichever occurred first. Of note, different criteria were used to assess GvHD within the study; aGvHD was graded according to two different criteria depending on the year of GvHD diagnosis.[10,11] Likewise, cGvHD was assessed according to two differing NIH criteria dependent on the year of cGvHD diagnosis.[12,13] Primary and secondary graft failure (GF) were defined according to EBMT criteria as not having reached 0.5×10^9/L absolute neutrophil count (ANC) by day +28 or ANC $<0.5 \times 10^9$/L after initial engraftment not related to relapse, infection or drug toxicity.

Statistical analysis

Clinical, demographic and transplantation-related characteristics at baseline were tabulated and compared between the four donor type groups using the χ^2 test for categorical variables and the Kruskal–Wallis test for continuous data. Baseline was defined as the day of allo-HCT infusion.

Median follow-up after baseline and 95% confidence intervals were calculated using the reverse Kaplan–Meier (KM) method. Time to neutrophil (first day of three consecutive days with $>0.5\times10^9$/L) and platelet (first of three consecutive days with $>20\times10^9$/L) engraftment was analysed using the cumulative incidence estimator (with death as a competing event), and Gray's test was used to compare the differences between groups. The primary end-point (OS) and secondary end-points (GRFS and RFS) were analysed using the KM estimator, and the log-rank test was used to assess the differences between groups. NRM together with CIR, aGvHD together with GF, second allo-HCT and death before aGvHD and cGvHD together with GF, second allo-HCT and death before cGvHD were analysed in a competing risk framework, and Gray's test was used to compare the differences between groups. Multivariable Cox proportional hazards models adjusted for potential confounders were fitted to assess the association between the donor type groups (MRD, MMRD, MUD and MMUD) and (1) engraftment (neutrophil and platelet engraftment), (2) GvHD (acute and chronic) and (3) outcome after allo-HCT (OS, RFS, relapse and NRM). Cause-specific hazard models were used for relapse, NRM, aGvHD, cGvHD, and neutrophil and platelet engraftment. All multivariable analyses (MVAs) were performed based on complete cases. Engraftment was censored if it occurred after 45 days in the neutrophil analysis and after 100 days in the platelet analysis. For aGvHD/death with aGvHD, outcomes were artificially censored at 100 days after allo-HCT, all other outcomes were artificially censored at 72 months after allo-HCT.

Apart from donor type, the following variables were included in the MVA and considered as potential confounders: patient age at allo-HCT, patient sex, graft source, type of conditioning (MAC and RIC), disease status at allo-HCT (CP1, CP ≥2, AP and BC), Karnofsky Performance Status (KPS), recipient cytomegalovirus (CMV) serostatus, year of allo-HCT and the time interval from diagnosis to allo-HCT. We checked whether the associations between risk factors and outcome after allo-HCT were similar across the four donor types by including an interaction term between donor type and known risk factors.

We tested for the subsistence of a possible centre effect using a random centre effect for each outcome in the MVA (using a normally distributed 'frailty' term). All statistical tests were two-sided, and significance was determined when $p\leq0.05$. All analyses were performed in R version 4.2.2[14]; using 'survival', 'cmprsk' and 'prodlim' packages.

RESULTS

The main baseline characteristics at the time of transplantation of the entire patient population alongside the four different donor type cohorts are shown in Table 1. Of the 1686 patients (from 271 centres) included in the study, 661 (39.2%) underwent allo-HCT from a MRD, 677 (40.2%) from a MUD, 212 (12.6%) from a MMUD and 136 (8%) from a MMRD. While the interval from diagnosis to allo-HCT was comparable between the four groups, age at allo-HCT was significantly lower in patients with related donors (median 44.3, IQR 35.1–52.8 years) than those with unrelated donors (UDs; median 47.1, IQR 36.1–56.2; $p=0.0002$). Allo-HCT was performed in CP in 70.3% of patients (CP1 in 43.4%, CP ≥2 in 26.9%), in AP in 11.7% and in BC in 17.9%. Of note, the majority of patients were transplanted in higher phases than CP1 (56.6%). BC accounted for a significantly higher percentage of patients undergoing allo-HCT with related donors (20.6%) when compared to those with UDs (15.2%; $p=0.01$). The highest percentage of patients undergoing allo-HCT in BC was in the MMRD group (26.1% vs. 14.4%–19.4% in the other three groups). Other significant differences between cohorts included stem cell source, which was BM derived in almost half (48.5%) of the MMRD cohort in comparison with between 10.4% and 14.3% in the other three donor cohorts (compared to all three combined $p<0.0001$), and the percentage of patients transplanted following a RIC regimen, representing 39.2% of patients in the MUD group and only 26.7% in the MRD group ($p<0.0001$). As expected, on average, MMRD allo-HCT was performed in more recent calendar years than transplants from other donor types, while the use of MMUD was relatively more frequent in earlier calendar years (Table 1).

Engraftment and GF

Engraftment outcomes are reported in Table 2. The cumulative incidence of both neutrophil ($\geq0.5\times10^9$/L) and platelet engraftment ($\geq20\times10^9$/L) significantly differed between the four groups (both $p<0.001$). Median time to both neutrophil and platelet engraftment was longer in the MMRD cohort than in other donor groups. Also in a MVA (Table 3), MMRD transplantations compared to allo-HCT utilizing MRD or MUD significantly associated with a longer time to neutrophil engraftment (hazard ratio [HR] MRD vs. MMRD 1.62 [95% CI 1.28–2.03] and MUD vs. MMRD 1.56 [95% CI 1.24–1.97]). Moreover, MMUD associated with a significantly longer time to neutrophil engraftment than MUD (HR 0.75, 95% CI 0.62–0.90). In addition, bone marrow (BM) as the source of stem cells, compared to peripheral blood (PB), was associated with a longer time to neutrophil engraftment in MVA (HR 0.49, 95% CI 0.41–0.57). For the MVA regarding platelet engraftment, MMRD significantly associated with a longer time to engraftment in comparison with all other donor types (HR MRD vs. MMRD 2.26 [95% CI 1.75–2.93], MUD vs. MMRD 2.15 [95% CI 1.67–2.78], and MMUD vs. MMRD 1.70 [95% CI 1.26–2.29]), and, similarly, in patients with a MMUD compared to MUD (HR 0.79, 95% CI 0.64–0.97). BM-derived stem cell source (HR vs. PB 0.58, 95% CI 0.48–0.70) and a KPS <90 (HR vs. ≥90 0.83, 95% CI 0.70–0.98) were associated with a longer time to platelet engraftment (Table 3). Finally, cumulative incidences of both primary ($p<0.001$) and secondary ($p=0.05$) GF significantly differed between the four cohorts (Table 2) and were highest in patients transplanted utilizing a MMRD (Table 2). Cumulative incidence of primary GF in the MMRD,

TABLE 1 Patient, disease and transplant characteristics.

	Total	MRD	MMRD	MUD	MMUD	
Characteristics	***N*** **(%)**	***N*** **(%)**	***N*** **(%)**	***N*** **(%)**	***N*** **(%)**	***p***
Total	1686 (100.0)	661 (100.0)	136 (100.0)	677 (100.0)	212 (100.0)	
Gender						
Male	1043 (61.9)	406 (61.4)	83 (61.0)	411 (60.7)	143 (67.5)	0.35
Female	643 (38.1)	255 (38.6)	53 (39.0)	266 (39.3)	69 (32.5)	
Interval diagnosis to allo-HCT (months)						
Median (IQR)	17.5 (8.8–37.2)	17.9 (8.4–38.4)	17.6 (10.0–42.2)	17.5 (8.6–35.7)	17.2 (10.1–34.1)	0.62
Age at allo HCT						
Median (IQR)	46 (36–55)	44 (35–53)	45 (34–53)	48 (37–57)	47 (35–54)	**<0.001**
Karnofsky PS at allo-HCT (missing $n = 104$)						
≥90	1240 (78.4)	482 (77.6)	95 (75.4)	511 (80.3)	152 (76.4)	0.42
<90	342 (21.6)	189 (22.4)	31 (24.6)	125 (19.7)	47 (23.6)	
Disease status at allo-HCT (missing $n = 33$)						
CP1	718 (43.4)	263 (40.9)	40 (29.9)	329 (49.3)	86 (41.3)	**<0.001**
CP ≥2	445 (26.9)	162 (25.2)	38 (28.4)	182 (27.2)	63 (30.3)	
AP	194 (11.7)	93 (14.5)	21 (15.7)	61 (9.1)	19 (9.1)	
BC	296 (17.9)	125 (19.4)	35 (26.1)	96 (14.4)	40 (19.2)	
Stem cell source						
BM	260 (15.4)	91 (13.8)	62 (45.6)	86 (12.7)	21 (9.9)	**<0.001**
PB	1418 (84.1)	567 (85.8)	70 (51.5)	591 (87.3)	190 (89.6)	
BM + PB	8 (0.5)	3 (0.5)	4 (2.9)		1 (0.5)	
Conditioning intensity (missing $n = 24$)						
MAC	1110 (66.8)	475 (73.3)	90 (66.7)	408 (60.8)	137 (65.9)	**<0.001**
RIC	552 (33.2)	173 (26.7)	45 (33.3)	263 (39.2)	71 (35.1)	
ATG prophylaxis given (missing $n = 2$)						
No	898 (53.3)	476 (72.1)	126 (92.6)	235 (34.8)	61 (28.8)	**<0.001**
Yes	786 (46.7)	184 (27.9)	110 (7.4)	441 (65.2)	151 (71.2)	
GvHD prophylaxis with PTCy						
No	1550 (91.9)	661 (100.0)		677 (100.0)	212 (100.0)	**<0.001**
Yes	136 (8.1)		136 (100.0)			
Year of allo-HCT						
2012–2015	957 (56.8)	381 (57.6)	51 (37.5)	384 (56.7)	141 (66.5)	**<0.001**
2016–2019	729 (43.2)	280 (42.4)	85 (62.5)	293 (43.3)	71 (33.5)	

Note: Bold character has been used to highlight statistically signficant findings.

Abbreviations: AP, accelerated phase; BC, blastic crisis; BM, bone marrow; CP ≥2, second or more than second chronic phase; CP1, first chronic phase; GvHD, graft-versus-host disease; HCT, haematopoietic cell transplantation; MAC, myeloablative conditioning; MMRD, mismatched related donor; MMUD, mismatched unrelated donor; MRD, matched related donor; MUD, matched unrelated donor; PB, peripheral blood; PS, performance score; PTCy, post-transplant cyclophosphamide; RIC, reduced intensity conditioning.

MMUD, MRD and MUD setting was 5.9%, 2.8%, 0.8% and 0.7% respectively.

For deceased patients (total number = 539), the cause of death—including GvHD and infections—according to donor type and the occurrence of primary and secondary GF is listed as a supplemental table in Supporting Information. Overall, 75% and 95% of patients with primary and secondary GF, respectively, died during the follow-up. Cause of death was mainly infection in patients with primary GF (72.2%), whereas in patients with secondary GF the distribution of the cause of death was more similar to patients who died without GF (Table S1).

GvHD

By univariable analysis, the cumulative incidence of aGvHD (grade II–IV) differed significantly between the four donor groups ($p = 0.003$). The 100-day cumulative incidence was highest (39%) in patients transplanted from a MMUD, 31% from a MUD, 26% from a MRD and was lowest (24%) in patients transplanted from a MMRD (Table 4; Figure 1). In MVA, however, there was only borderline evidence that the risk of aGvHD was different between the four groups ($p = 0.06$), with the highest risk in patients transplanted from

TABLE 2 Engraftment outcomes according to the type of donor.

	MRD	MMRD	MUD	MMUD	*p*
Days ANC $>0.5\times10^9$/L, median (IQR)	16 (14–19)	19 (16–24)	16 (13–20)	16 (14–20)	**<0.001**
Days PLT $>20\times10^9$/L, median (IQR)	15 (12–20)	27 (19–34)	15 (12–21)	15 (12–23)	**<0.001**
28-day cumulative incidence of primary graft failure	0.8% (0.1–1.4)	5.9% (1.9–9.8)	0.7% (0.1–1.4)	2.8% (0.6–5.1)	**<0.001**
4-year cumulative incidence of secondary graft failure (95% CI)	5% (3–7)	10% (4–15)	3% (2–5)	1% (0–3)	**0.05**

Note: Estimates of the cumulative incidence of primary and secondary graft failure and median time to neutrophil and platelet recovery were obtained using the crude cumulative incidence estimator with death as a competing event, *p*-values were obtained using Grey's test. Bold character has been used to highlight statistically signficant findings.

Abbreviations: ANC, absolute neutrophil count; CI, confidence interval; MMRD, mismatched related donor; MMUD, mismatched unrelated donor; MRD, matched related donor; MUD, matched unrelated donor; PLT, platelet count.

a MMUD. The only significant association observed among confounders was a lower risk of aGvHD with later calendar years of allo-HCT with a HR of 0.94 (95% CI 0.90–0.98) per year later (Table 3). The cumulative incidence of cGvHD was significantly different between the four groups ($p=0.01$) in the univariable analysis and was lowest in the MMRD setting (30% at 24 months and 34% at 48 months respectively) (Table 4; Figure 2). Significant differences between donor type remained in the MVA (overall $p=0.01$) with a significantly higher risk of cGvHD in patients transplanted with MRD or MMUD than with MUD (HR 1.35, 95% CI 1.10–1.65, and HR 1.40, 95% CI 1.06–1.85 respectively). No other baseline characteristics were independently associated with the risk of cGvHD (Table 3).

Allo-HCT outcomes

With a median follow-up time of 35.4 months (IQR 12.5–64.1), the 4 year OS and RFS estimates in the entire patient population were 61% (95% CI 58–64) and 49% (95% CI 46–52) respectively (Figure S1a,b), with a 4-year CIR and NRM of 31% (95% CI 28–33) and 20% (95% CI 18–23) respectively (Figure S1c). Four-year GRFS estimate was 18% (95% CI 16–21) (Figure S1d). Table 5 summarizes the results of univariable analyses by OS, RFS, CIR and NRM at 4 years following allo-HCT also for other baseline characteristics. No statistically significant differences according to donor type were found for OS, CIR and NRM. In contrast, RFS (log-rank $p=0.03$) and the combined end-point of GRFS (log-rank $p=0.05$) were significantly different between the four groups with patients transplanted from a MUD showing the best outcomes in comparison with other groups (Figure 2; Table 5). Age at allo-HCT <50 years, KPS ≥90%, disease status at allo-HCT, recipient CMV seronegativity, BM as the donor stem cell source and MAC were significantly associated with better OS. The same factors except age at the time of allo-HCT and BM source were significantly associated with better RFS. A higher CIR was observed in patients with KPS <90 (4-year cumulative incidence 41% vs. 29%), and more advanced disease stage at time of transplant (log-rank $p<0.001$). The cumulative incidence of NRM was significantly higher in patients aged ≥50 years (25% vs. 18%), male recipients with a female donor (27% vs. 19% in other donor/recipient combinations), in patients having a KPS <90% (25% vs. 19%), transplanted with PB derived stem cells (22% vs. 14% in marrow derived stem cells) and undergoing a RIC allo-HCT (24% vs. 18% in MAC). Univariable analyses of donor type per 4-year period of allo-HCT on OS, RFS, CIR and NRM are shown in Table 5 and in Supporting Information (Figure S2a–d). Overall, better outcomes in patients undergoing allo-HCT were observed in the later calendar 4-year period (2016–2019), except in those with MRD, in whom a higher CIR—though not statistically significant (log-rank $p=0.06$)—was observed during the 2016–2019 period.

When MVA were adjusted for other factors, however, no significant differences in OS, RFS, relapse risk and NRM were evident between the four donor groups (Table 6). However, due to the small number of MMRD patients, the 95% confidence interval was wide. For OS, the estimates were with a HR for MRD versus MMRD of 0.89 (95% CI 0.62–1.27), HR for MUD versus MMRD of 0.89 (95% CI 0.62–1.28) and HR for MMUD versus MMRD of 0.95 (95% CI 0.63–1.24).

We tested for differences between centres in the risk of outcomes after allo-HCT. There was no evidence for such a difference for OS ($p=0.31$), RFS ($p=0.27$) or NRM ($p=0.15$), while a borderline significant difference was identified for relapse ($p=0.04$). As the donor type estimates obtained with models with and without random centre effect were similar, estimates are based on models without centre effect.

Factors associated with worse OS, RFS and higher risk of relapse were low PS (KPS <90%) and more advanced disease stage. Low KPS (HR for KPS <90 vs. ≥90 1.48, 95% CI 1.11–1.99) and higher age at time of allo-HCT (HR per 10-year increase 1.17, 95% CI 1.04–1.31) also associated with higher risk of NRM. Among other covariates, older age at allo-HCT (HR 1.13 per 10-year increase) and recipient CMV seropositive status (HR 1.25 in comparison with CMV-negative) were also associated with poorer OS, whereas the use of RIC associated with worse RFS (HR vs. MAC 1.24, 95% CI 1.-4–1.49) and higher risk of relapse (HR 1.30, 95% CI 1.03–1.64). Using BM as stem cell source (HR vs. PB 0.62, 95% CI 0.40–0.95)

TABLE 3 Risk estimates of the association between baseline characteristics and neutrophils/platelets engraftment, acute graft-versus-host disease (aGvHD) and chronic graft-versus-host disease (cGvHD) obtained using multivariable Cox (cause-specific) proportional hazards models.

	Neutr $<0.5\times10^9$/L		PLT $>20\times10^9$/L		aGvHD		cGvHD	
	HR[a] (95% CI)	(overall) *p*	HR[a] (95% CI)	(overall) *p*	HR (95% CI)	(overall) p	HR (95% CI)	(overall) *p*
Donor type		(**<0.0001**)		(**<0.0001**)		(0.06)		(**0.01**)
MRD versus MMRD	1.62 (1.28–2.03)	**<0.0001**	2.26 (1.75–2.93)	**<0.0001**	0.89 (0.59–1.33)	0.56	1.28 (0.87–1.91)	0.21
MUD versus MMRD	1.56 (1.24–1.97)	**0.0002**	2.15 (1.67–2.78)	**<0.0001**	1.03 (0.68–1.55)	0.89	0.95 (0.64–1.42)	0.82
MMUD versus MMRD	1.17 (0.89–1.53)	0.25	1.70 (1.26–2.29)	**0.0005**	1.33 (0.85–2.10)	0.21	1.34 (0.86–2.08)	0.19
MRD versus MUD	1.03 (0.91–1.18)	0.61	1.05 (0.91–1.22)	0.50	0.86 (0.69–1.08)	0.19	1.35 (1.10–1.65)	**0.004**
MMUD versus MUD	0.75 (0.62–0.90)	**0.002**	0.79 (0.64–0.97)	**0.03**	1.30 (0.97–1.72)	0.08	1.40 (1.06–1.85)	**0.02**
Age at allo-HCT (per 10-year increase)	1.06 (1.01–1.11)	**0.02**	1.06 (1.01–1.13)	**0.03**	0.95 (0.88–1.03)	0.25	0.99 (0.91–1.07)	0.74
Source of SC								
BM versus PB	0.49 (0.41–0.57)	**<0.0001**	0.58 (0.48–0.70)	**<0.0001**	0.81 (0.60–1.10)	0.17	0.81 (0.63–1.05)	0.11
Karnofsky PS								
<90% versus ≥90%	0.90 (0.78–1.03)	0.13	0.83 (0.70–0.98)	**0.03**	0.99 (0.78–1.26)	0.94	1.03 (0.82–1.30)	0.78
Disease status at allo-HCT		(0.42)		(0.20)		(0.28)		(0.12)
≥CP2 versus CP1	0.98 (0.86–1.13)	0.82	1.12 (0.96–1.32)	0.16	1.03 (0.81–1.31)	0.80	1.06 (0.86–1.31)	0.58
AP versus CP1	0.86 (0.71–1.05)	0.145	0.88 (0.70–1.11)	0.28	1.35 (1.00–1.83)	**0.05**	0.83 (0.61–1.13)	0.25
BC versus CP1	1.03 (0.87–1.21)	0.74	0.97 (0.81–1.17)	0.78	1.02 (0.77–1.35)	0.89	0.78 (0.59–1.03)	0.08
AP versus BC	0.84 (0.68–1.05)	0.12	0.91 (0.70–1.17)	0.45	1.33 (0.93–1.89)	0.11	1.87 (0.74–1.54)	0.72
Recipient CMV status at allo-HCT								
Positive versus negative	0.94 (0.83–1.06)	0.31	0.89 (0.78–1.02)	0.10	0.81 (0.71–1.06)	0.17	0.99 (0.82–1.20)	0.94
Conditioning intensity								
RIC versus MAC	1.01 (0.89–1.16)	0.84	1.07 (0.92–1.25)	0.37	0.98 (0.78–1.24)	0.89	0.85 (0.68–1.05)	0.13
Year of allo-HCT (per year later)	1.01 (0.99–1.04)	0.31	1.01 (0.98–1.04)	0.66	0.94 (0.90–0.98)	**0.003**	0.97 (0.93–1.01)	0.12

Note: Overall *p*-values were obtained with the likelihood ratio test. Bold character has been used to highlight statistically signficant findings.

Abbreviations: AP, accelerated phase; BC, blastic crisis; BM, bone marrow; CMV, cytomegalovirus; CP ≥2, second or more than second chronic phase; CP1, first chronic phase; HR, hazard ratio; MAC, myeloablative conditioning; MMRD, mismatched related donor; MMUD, mismatched unrelated donor; MRD, matched related donor; MUD, matched unrelated donor; PB, peripheral blood; PS, performance score; RIC, reduced intensity conditioning.

[a]For engraftment outcomes, lower HR's mean a longer time to engraftment.

TABLE 4 Grade II–IV acute and chronic GvHD according to the donor type.

Cumulative incidence	MRD	MMRD	MUD	MMUD	*p*
Day 100 acute GvHD, % (95% CI)	26% (23–30)	24% (17–32)	31% (27–34)	39% (32–46)	**0.003**
24-month chronic GvHD, % (95% CI)	43% (39–47)	30% (21–38)	35% (31–39)	42% (35–49)	**0.01**
48-month chronic GvHD, % (95% CI)	45% (41–50)	34% (24–44)	37% (33–41)	43% (36–51)	

Note: Cumulative incidence of acute and chronic GvHD was obtained using the crude cumulative incidence estimator (with death, second allo-HCT and primary graft failure as competing events), *p*-values were obtained using Gray's test. Bold character has been used to highlight statistically signficant findings.

Abbreviations: CI, confidence interval; GvHD, graft-versus-host disease; HCT, haematopoietic cell transplantation; MMRD, mismatched related donor; MMUD, mismatched unrelated donor; MRD, matched related donor; MUD, matched unrelated donor.

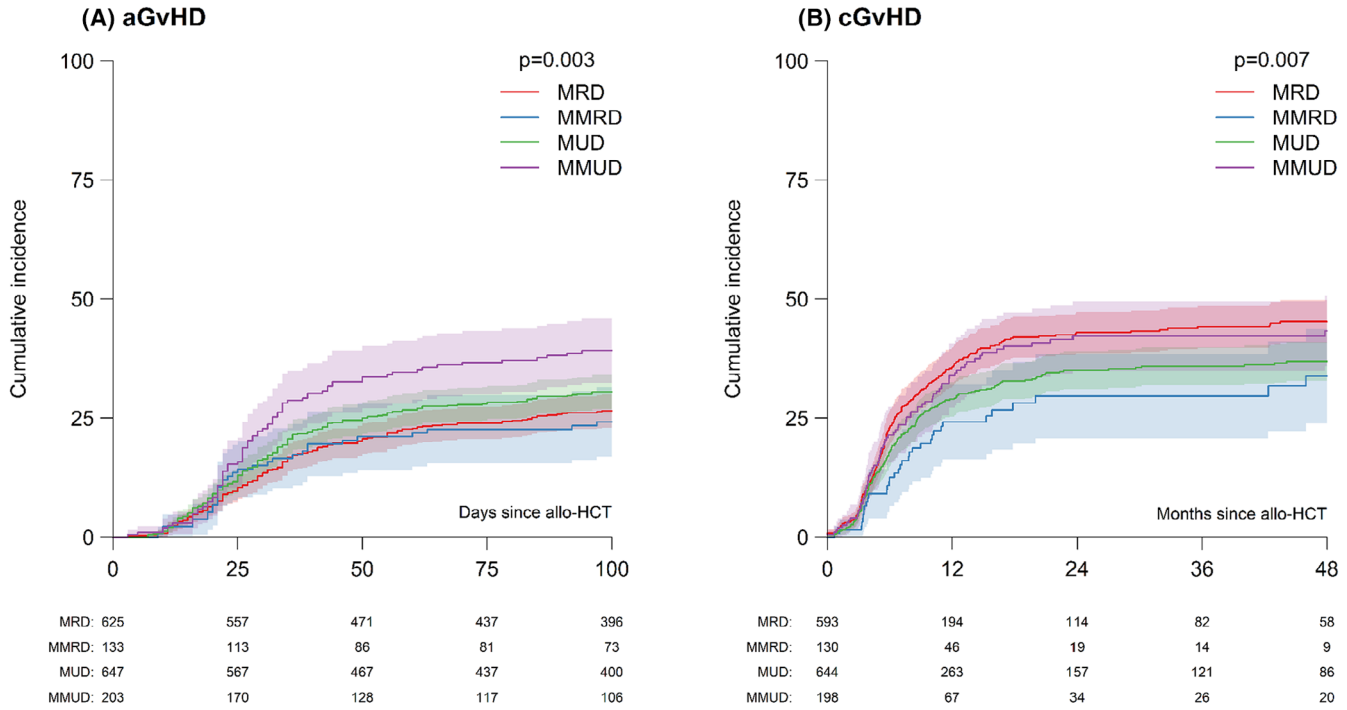

FIGURE 1 Cumulative incidence of graft-versus-host disease (GvHD) after allo-haematopoietic cell transplantation (HCT), (A) acute GvHD (aGvHD) and (B) chronic GvHD (cGvHD). Shaded areas represent the 95% confidence intervals. The figures below the graph are the number of patients at risk. MMRD, mismatched related donor; MMUD, mismatched unrelated donor; MRD, matched related donor; MUD, matched unrelated donor.

and transplantations in more recent calendar years (HR per year later 0.93, 95% CI 0.87–0.98) associated with a reduced risk of NRM (Table 6).

With regard to the cause of death different from relapse/progression, infections were more frequently reported in patients transplanted with MMRD (36.7%) in comparison with other donor groups (19.4%, 23.6% and 22.1% in MRD, MUD and MMUD, respectively), whereas GvHD was less frequently reported (16.3% in MMRD vs. 31.3%, 27.8% and 33.8% in MRD, MUD and MMUD respectively) (Table S1).

Finally, we checked whether the observed associations of risk factors and outcome after allo-HCT were similar across the different donor types. There was a significant interaction between donor type and disease phase at allo-HCT for both RFS and risk of relapse, with interaction *p*-values of 0.03 and 0.04 respectively. The interaction was driven by patients with MMUD in AP and MMRD in BC, who appeared to have a lower risk compared to patients with a MRD or MUD while in the same disease phase (Table S2).

DISCUSSION

This retrospective registry-based study from the EBMT included a very large series of CML patients undergoing allo-HCT over an 8-year period, including almost 80% utilizing a graft from a related or unrelated HLA-fully matched donor and 8% from a MMRD.

Prior to the introduction of TKI into the treatment algorithm, allo-HCT was the only curative option for CML, representing the treatment of choice for eligible patients in all disease phases. Although the introduction of TKIs has led to a profound and rapid change in the treatment paradigm, allo-HCT remains the favoured option for most patients in advanced disease stage and the best cure opportunity for a selection of patients in CP with TKI resistance. Indeed, the last EBMT activity report prior to the COVID-19 pandemic described an overall 6.2% increase in transplanted patients for CML in 2019, when compared to 2018 (14.4% decrease in CP1 and 30.6% increase in advanced phase disease).[9] As far

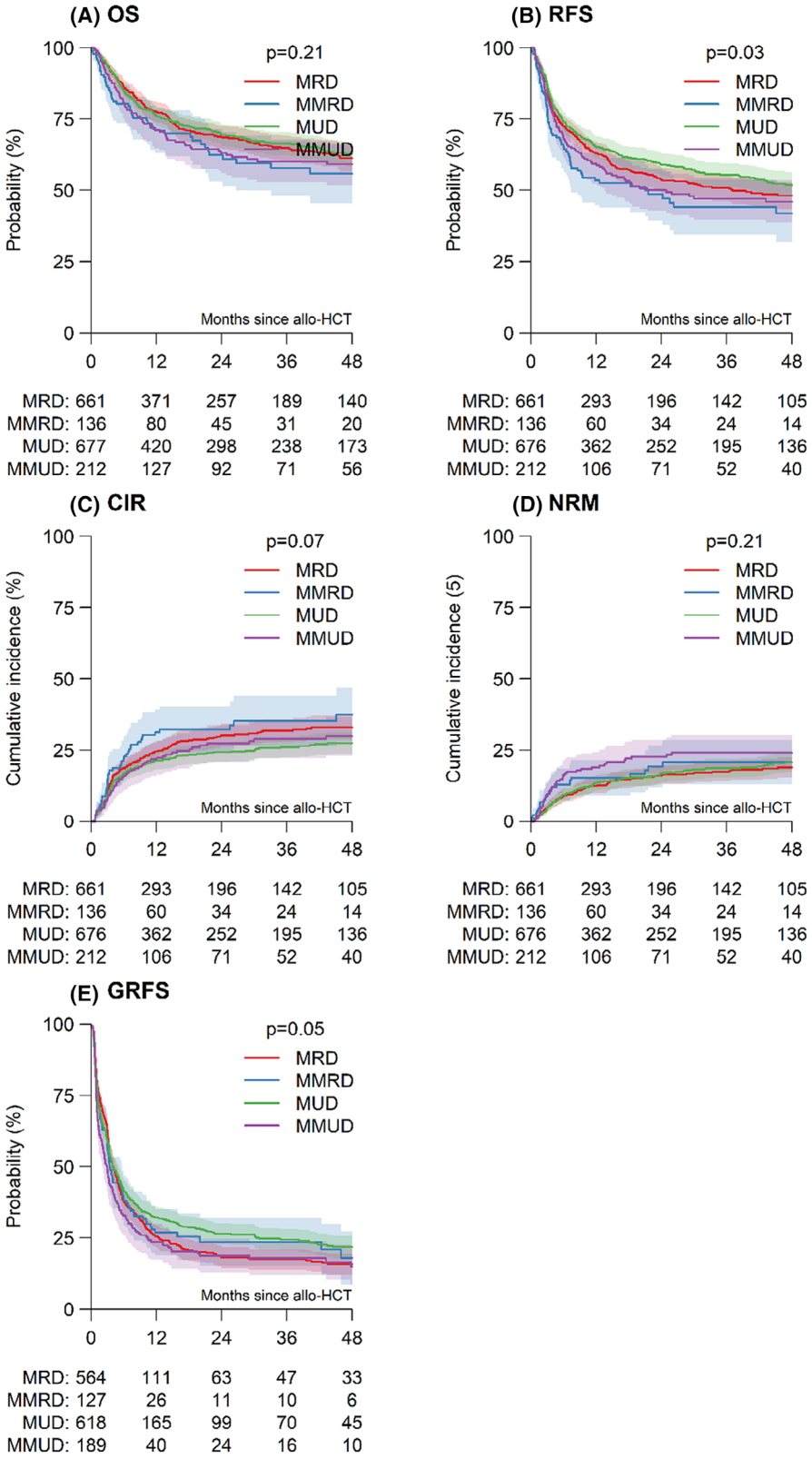

FIGURE 2 Outcome after allo-haematopoietic cell transplantation (HCT), (A) overall survival (OS), (B) relapse-free/progression-free survival (RFS), (C) cumulative incidence of relapse (CIR), (D) cumulative incidence of non-relapse mortality (NRM) and (E) combined graft-versus-host disease/relapse-free survival (GRFS) of patients according to the type of donor used as part of the allo-HCT. Shaded areas represent the 95% confidence intervals. The figures below the graph are the number of patients at risk. MMRD, mismatched related donor; MMUD, mismatched unrelated donor; MRD, matched related donor; MUD, matched unrelated donor.

TABLE 5 Univariate analysis of the association of baseline characteristics with overall survival (OS), relapse-free survival (RFS), cumulative incidence of relapse (CIR) and non-relapse mortality (NRM).

Factor	4-year OS (95% CI)	*p*	4-year RFS (95% CI)	*p*	4-year CIR (95% CI)	*p*	4-year NRM (95% CI)	*p*
Donor type								
MRD	61% (57–66%)	0.21	48% (43–53%)	**0.03**	33% (29–37%)	0.07	19% (15–23%)	0.21
MMRD	56% (45–66%)		42% (32–52%)		37% (28–47%)		21% (13–28%)	
MUD	63% (58–67%)		52% (47–56%)		27% (24–31%)		21% (17–24%)	
MMUD	59% (52–67%)		46% (39–53%)		30% (23–37%)		24% (18–30%)	
Patient sex								
Male	60% (56–64%)	0.33	47% (43–50%)	0.08	32% (29–36%)	0.06	21% (18–24%)	0.90
Female	63% (59–68%)		53% (48–57%)		28% (24–32%)		20% (16–23%)	
Age at allo-HCT (years)								
<50	65% (62–69%)	**0.001**	51% (47–54%)	0.08	32% (28–35%)	0.71	18% (15–21%)	**0.01**
≥50	55% (51–60%)		46% (42–51%)		29% (25–33%)		25% (21–28%)	
Donor/recipient sex								
F/M	60% (54–66%)	0.60	48% (41–54%)	0.83	25% (20–30%)	0.09	27% (21–33%)	**0.02**
Other comb.	61% (58–65%)		49% (46–52%)		32% (29–35%)		19% (16–21%)	
Interval diagnosis to allo-HCT								
<9 months	62% (59–66%)	0.34	49% (46–53%)	0.50	30% (27–32%)	0.06	21% (19–24%)	0.18
≥9 months	58% (53–64%)		48% (42–53%)		34% (29–39%)		18% (14–23%)	
Source of SC								
PB	60% (57–63%)	**0.04**	49% (45–52%)	0.53	30% (27–32%)	0.24	22% (19–24%)	**0.03**
BM	67% (60–73%)		51% (44–58%)		35% (29–42%)		14% (10–19%)	
Karnofsky PS								
≥90	66% (63–69%)	**<0.001**	52% (49–56%)	**<0.001**	29% (26–31%)	**<0.001**	19% (17–22%)	**0.05**
<90	44% (37–50%)		34% (27–40%)		41% (35–48%)		25% (19–30%)	
Disease status at allo-HCT								
CP1	71% (67–75%)	**<0.001**	58% (53–62%)	**<0.001**	22% (19–26%)	**<0.001**	20% (16–23%)	0.59
≥CP2	60% (54–65%)		44% (39–50%)		34% (29–40%)		22% (17–26%)	
AP	57% (48–65%)		47% (39–55%)		34% (26–41%)		19% (13–26%)	
BC	43% (36–50%)		36% (29–42%)		43% (37–49%)		21% (16–27%)	
CMV status at allo-HCT in patient								
Negative	67% (63–72%)	**0.002**	51% (47–56%)	**0.03**	29% (25–33%)	0.13	19% (16–23%)	0.34
Positive	58% (55–62%)		48% (44–51%)		32% (29–35%)		20% (17–23%)	
Conditioning type								
MAC	65% (62–68%)	**0.002**	52% (49–56%)	**<0.001**	30% (27–33%)	0.06	18% (15–21%)	**0.04**
RIC	55% (50–60%)		43% (39–48%)		32% (28–37%)		24% (20–28%)	
Donor type/calendar year period								
MRD 2012–2015	64% (64–74%)	0.35	50% (44–56%)	0.37	30% (25–35%)	0.06	20% (15–24%)	0.31
MRD 2016–2019	55% (46–65%)		45% (36–54%)		36% (29–43%)		19% (12–27%)	
MMRD 2012–2015	53% (39–67%)	0.55	40% (26–54%)	0.57	38% (25–52%)	0.76	22% (10–33%)	0.74

(Continues)

TABLE 5 (Continued)

Factor	4-year OS (95% CI)	*p*	4-year RFS (95% CI)	*p*	4-year CIR (95% CI)	*p*	4-year NRM (95% CI)	*p*
MMRD 2016–2019	60% (46–74%)		43% (29–58%)		36% (23–49%)		21% (9–32%)	
MUD 2012–2015	61% (55–66%)	0.05	50% (44–55%)	0.08	29% (24–34%)	0.42	22% (17–26%)	0.22
MUD 2016–2019	64% (54–73%)		55% (46–64%)		24% (18–29%)		21% (13–30%)	
MMUD 2012–2015	56% (47–65%)	0.17	42% (34–51%)	0.13	29% (21–37%)	0.84	29% (21–36%)	0.04
MMUD 2016–2019	66% (53–80%)		55% (41–68%)		32% (19–45%)		14% (5–22%)	

Note: OS and PFS estimates were obtained using the Kaplan–Meier estimator, and comparisons were made using the log-rank test. Cumulative incidence of NRM and progression/relapse estimates were obtained using the crude cumulative incidence estimator and groups were compared using Gray's test. Bold character has been used to highlight statistically signficant findings.

Abbreviations: AP, accelerated phase; BC, blastic crisis; BM, bone marrow; CI, confidence interval; CMV, cytomegalovirus; CP ≥2, second or more than second chronic phase; CP1, first chronic phase; HCT, haematopoietic cell transplantation; MAC, myeloablative conditioning; MMRD, mismatched related donor; MMUD, mismatched unrelated donor; MRD, matched related donor; MUD, matched unrelated donor; PB, peripheral blood; PS, performance score; RIC, reduced intensity conditioning.

as the type of donor is concerned, following the introduction of PTCy as a feasible and effective platform for GvHD prophylaxis in replacement of ex-vivo T-cell depletion,[10] the number of allo-HCT from MMRD for all haematological malignancies, including CML, has rapidly increased over the years, particularly after 2012.[9]

In our study, univariable analysis displayed that patients undergoing allo-HCT with a MMRD had an inferior 4-year RFS in comparison with MRD but not to either MUD or MMUD. This worse outcome was partly due to the higher percentage of patients with more advanced disease undergoing allo-HCT with a MMRD. Following adjustment for disease stage and other covariates in MVA, differences in the combined risk of relapse/progression and death were not significant. We observed a lower cumulative incidence of acute and cGvHD in the univariable analysis for the MMRD group in comparison with MRD and MMUD. Following adjustment for confounders in the MVA, however, there was no difference in the risk of aGvHD and cGvHD between the MMRD group and the other donor groups. Indeed, univariable results were partly confounded by the differences between the MMRD group and other types groups, in particular with regard to the stem cell source and the year of allo-HCT. Further to this context, it is worth noting that patients transplanted using MRD, MUD or MMUD who received PTCy were intentionally excluded in our study to avoid bias associated with the GvHD prophylaxis strategy when comparing the outcomes of allo-HCT by donor type. As such, we can speculate that the use of PTCy—which was used in 100% of the patients transplanted from MMRD included in this study—could entirely explain the lower cumulative incidence of acute and cGvHD in this group of patients observed within the univariable analysis. However, the lack of independence unveiled with the adjustment for other covariates which were significantly more frequent in the MMRD group—mainly the use of BM as the stem cell source in a higher proportion of cases and the more recent year of transplantation does not facilitate confirmation of that hypothesis.

In line with the results of our analysis, another recently published retrospective study from our EBMT-CMWP comparing PTCy-based versus non-PTCy-based allo-HCT from an UD and PTCy allo-HCT from a MMRD in patients with CML reported no significant differences between the three cohorts regarding OS, RFS, RI and NRM.[8]

In our study, with regard to the observed higher risk of cGvHD in patients transplanted from MRD in comparison with MUD, we verified a lower use of ATG in the former group, which may at least partially explain such unexpected finding. Indeed, when included in the MVA, the MRD versus MUD HR was still statistically significant but closer to 1 (from 1.35, 95% CI 1.10–1.65 to 1.27, 95% CI 1.02–1.57).

The more frequent use of BM as stem cell source in patients undergoing allo-HCT with a MMRD compared to the other donor type groups did not fully explain the observed longer time to engraftment in the MMRD cohort. On MVA, patients transplanted from MMRD had a significantly lower chance of reaching engraftment reflecting a longer time to both neutrophil and platelet count recovery in patients with MMRD compared to both MRD and MUD. The significantly higher use of BM as stem cell source may also contribute to the observed augmented risk of GF in the MMRD allo-HCT cohort. A higher risk of GF was reported by Orti et al. as well for those patients undergoing MMRD with PTCy compared to UD PTCy/non-PTCy prophylaxis cohorts.[8] It is worth mentioning that in both studies, KPS <90

TABLE 6 Risk estimates of the association between baseline characteristics and overall survival (OS), relapse-free survival (RFS), and the risk of relapse (REL) and non-relapse mortality (NRM) obtained using multivariable Cox (cause-specific) proportional hazards models.

	OS		RFS		CIR		NRM	
	HR (95% CI)	**(overall) *p***	**HR (95% CI)**	**(overall) *p***	**HR (95% CI)**	**(overall) *p***	**HR (95% CI)**	**(overall) *p***
Donor type		(0.89)		(0.40)		(0.44)		(0.51)
MRD versus MMRD	0.89 (0.62–1.27)	0.51	0.92 (0.68–1.25)	0.61	1.04 (0.72–1.50)	0.83	0.75 (0.45–1.28)	0.29
MUD versus MMRD	0.89 (0.62–1.28)	0.52	0.82 (0.60–1.11)	0.19	0.86 (0.59–1.26)	0.44	0.74 (0.44–1.25)	0.26
MMUD versus MMRD	0.95 (0.63–1.44)	0.81	0.93 (0.66–1.32)	0.68	0.92 (0.59–1.43)	0.70	0.92 (0.52–1.65)	0.79
MRD versus MUD	1.00 (0.81–1.24)	1.00	1.13 (0.94–1.36)	0.18	1.21 (0.96–1.52)	0.11	1.02 (0.76–1.37)	0.91
Age at allo-HCT (per 10-year increase)	1.13 (1.04–1.22)	**0.003**	1.04 (0.97–1.12)	0.24	0.97 (0.89–1.06)	0.53	1.17 (1.04–1.31)	**0.007**
Source of SC								
BM versus PB	0.80 (0.60–1.07)	0.13	1.02 (0.81–1.28)	0.88	1.31 (1.00–1.72)	0.06	0.62 (0.40–0.95)	**0.03**
Karnofsky PS								
<90% versus ≥90%	1.81 (1.48–2.21)	**<0.0001**	1.53 (1.28–1.82)	**<0.0001**	1.55 (1.24–1.94)	**0.0001**	1.48 (1.11–1.99)	**0.008**
Disease status at allo-HCT		**(<0.0001)**		**(<0.0001)**		**(<0.0001)**		(0.44)
≥CP2 versus CP1	1.53 (1.20–1.94)	**0.0005**	1.44 (1.19–1.75)	**0.0002**	1.59 (1.23–2.05)	**0.004**	1.26 (0.93–1.71)	0.14
AP versus CP1	1.74 (1.28–2.35)	**0.0004**	1.38 (1.06–1.79)	**0.02**	1.63 (1.17–2.26)	**0.005**	1.07 (0.69–1.66)	0.75
BC versus CP1	2.29 (1.79–2.93)	**<0.0001**	1.84 (1.48–2.28)	**<0.0001**	2.32 (1.77–3.03)	**<0.0001**	1.25 (0.87–1.80)	0.23
AP versus BC	0.76 (0.56–1.03)	**0.08**	0.75 (0.57–0.99)	**0.05**	0.70 (0.50–0.99)	**0.04**	0.86 (0.53–1.40)	0.54
Recipient CMV status at allo-HCT								
Positive versus negative	1.25 (1.02–1.54)	**0.03**	1.11 (0.94–1.32)	0.22	1.08 (0.87–1.34)	0.49	1.15 (0.88–1.52)	0.30
Conditioning intensity								
RIC versus MAC	1.14 (0.93–1.41)	0.21	1.24 (1.04–1.49)	**0.02**	1.30 (1.03–1.64)	**0.02**	1.15 (0.86–1.53)	0.36
Year of allo-HCT (per year later)	0.97 (0.92–1.01)	0.12	0.98 (0.94–1.02)	0.25	1.01 (0.97–1.06)	0.64	0.93 (0.87–0.98)	**0.01**

Note: Overall *p*-values were obtained with the likelihood ratio test. Bold character has been used to highlight statistically signficant findings.

Abbreviations: AP, accelerated phase; BC, blastic crisis; BM, bone marrow; CI, confidence interval; CMV, cytomegalovirus; CP ≥2, second or more than second chronic phase; CP1, first chronic phase; HCT, haematopoietic cell transplantation; HR, hazard ratio; MAC, myeloablative conditioning; MMRD, mismatched related donor; MMUD, mismatched unrelated donor; MRD, matched related donor; MUD, matched unrelated donor; PB, peripheral blood; PS, performance score; RIC, reduced intensity conditioning.

and advanced disease status were identified among factors independently associated with worse OS and RFS.

Of particular interest is also the observation of a significantly higher percentage of patients transplanted in advanced disease phases (AP+ higher CP) in the MMRD group (41.8%) in comparison with other groups (33.9% in MRD, 23.5% in MUD, 28.3% in MMUD), which suggests that in patients with CML the choice of donor type is a direct consequence of the transplant urgency. In such context, the finding of a statistically significant interaction term between donor type and disease phase resulting in a lower risk of relapse and a better RFS in patients transplanted by mismatched in comparison with matched donors raises the question whether the HLA mismatching may actually lead to a stronger GvL effect.

With regard to the conditioning type, the higher selection of RIC regimens in patients transplanted from MUD when compared to other groups is possibly explained by both the higher median age and the lower fraction of patients with advanced disease phases.

The limited size of the MMRD group, resulting in wide confidence intervals in our estimates, is a limitation of this study. It does not allow to offer guidelines on donor type decisions and we cannot rule out that clinically important differences between MMRD and other donor groups exist. Future studies including larger patient population with longer follow-up may therefore provide further important information guiding donor type decisions in CML patient candidate for allo-HCT.

In conclusion, we found that the utilization of a MMRD represents a potentially feasible option for patients undergoing allo-HCT for CML in the absence of better options, with no statistical evidence of a difference in survival outcomes, CIR and NRM in comparison with other donor types. Similarly, we did not observe a significant difference in the risk of developing acute or cGvHD when comparing patients transplanted from MMRD with other donor type groups. Most importantly, both MMRD allo-HCT and the use of BM as the stem cell source were significantly associated with longer times to neutrophil and platelet engraftment, and MMRD allo-HCT associated with higher risk of GF. Finally, we confirm that more advanced disease stage is a major factor impacting upon OS and RFS and that it is of utmost importance to bring CML patients with a transplant indication to allo-SCT in CP1 and avoid as much as possible patients progressing to higher disease phases before deciding on allo-HCT.

AUTHOR CONTRIBUTIONS

Francesco Onida and Luuk Gras had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Francesco Onida, Yves Chalandon, Donal P. McLornan. Acquisition, analysis, or interpretation of data: Francesco Onida, Luuk Gras, Linda Koster, Yves Chalandon, and Donal P. McLornan. Statistical analysis: Luuk Gras and Junran Ge. Drafting of the manuscript: Francesco Onida, Luuk Gras, Yves Chalandon, Donal P. McLornan. Critical revision of the manuscript for important intellectual content: Rose-Marie Hamladji, Jenny Byrne, Daniele Avenoso, Mahmoud Aljurf, Marie Robin, Kazimierz Halaburda, Jakob Passweg, Urpu Salmenniemi, Henrik Sengeloev, Jane Apperley, Andrew Clark, Péter Reményi, Elena Morozova, Francesca Kinsella, Stig Lenhoff, Arnold Ganser, Ka Lung Wu, Antonio Perez-Martinez, Patrick J. Hayden, Kavita Raj, Joanna Drozd-Sokolowska, Guillermo Orti, Hugues de Lavallade, Ibrahim Yakoub-Agha.

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ACKNOWLEDGEMENTS

We thank all the centres that report data to the EBMT contributing to this study, all those who have worked on the data registry, the health team that cared for the patients and all the patients.

CONFLICT OF INTEREST STATEMENT

Francesco Onida, Luuk Gras, Junran Ge, Linda Koster, Rose-Marie Hamladji, Mahmoud Aljurf, Marie Robin, Kazimierz Halaburda, Jakob Passweg, Urpu Salmenniemi, Henrik Sengeloev, Jane Apperley, Andrew Clark, Péter Reményi, Elena Morozova, Francesca Kinsella, Stig Lenhoff, Arnold Ganser, Ka Lung Wu, Antonio Perez-Martinez, Patrick J. Hayden, Kavita Raj, Joanna Drozd-Sokolowska, Hugues de Lavallade, Ibrahim Yakoub-Agha and Donal P. McLornan have no conflicts of interest to declare. Jenny Byrne served in the advisory boards for Incyte and Novartis. Daniele Avenoso received speaking fee from Incyte. Guillermo

Orti received consulting fees from BMS, Incyte, Norvartis and Pfizer; travel support from BMS, Incyte, Norvartis and Pfizer; institutional research grant from Incyte; and honoraria from BMS, Incyte, Jazz, Norvartis and Pfizer. Yves Chalandon received consulting fees from MSD, Novartis, Incyte, BMS, Pfizer, AbbVie, Roche, Jazz, Gilead, Amgen, AstraZeneca, Servier and travel support from MSD, Roche, Gilead, Amgen, Incyte, AbbVie, Janssen, AstraZeneca and Jazz.

ETHICS STATEMENT

The EBMT is a non-profit scientific society representing more than 600 transplant centres mainly in Europe. EBMT centres commit to obtain informed consent according to the local regulations applicable at the time in order to report pseudonymized data stored in a central database.

DATA AVAILABILITY STATEMENT

As per EBMT Policy, data cannot be shared but will be made available on reasonable request to the Chronic Malignancies Working Party of the EBMT.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Onida F, Gras L, Ge J, Koster L, Hamladji R-M, Byrne J, et al. Mismatched related donor allogeneic haematopoietic cell transplantation compared to other donor types for Ph+ chronic myeloid leukaemia: A retrospective analysis from the Chronic Malignancies Working Party of the EBMT. Br J Haematol. 2024;204(6):2365–2377. https://doi.org/10.1111/bjh.19448