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ARTICLE

STEM CELL TRANSPLANTATION

Older MRD vs. younger MUD in patients older than 50 years with AML in remission using post-transplant cyclophosphamide

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An increasing number of older patients with acute myeloid leukemia (AML) are offered an allogeneic hematopoietic stem cell transplantation (allo-HSCT). Normally, older patients have older matched related donors (MRD). Matched unrelated donors (MUD) are an important alternative, but it remains unclear whether a younger MUD is associated with better outcomes, especially in the context of post-transplant cyclophosphamide (PTCy). We compared outcomes of patients older than 50 years with AML in first complete remission (CR1) and receiving a first HSCT from a 10/10 MUD aged younger than 40 years to those receiving a graft from a MRD aged older than 50 years, using PTCy and with well-known transplant conditioning intensity (TCI) score. A total of 345 consecutive patients were included and classified according to TCI score as low, intermediate, or high. On multivariable analysis in the TCI-intermediate/high group, MUD was associated with better graft-versus-host disease-free, relapse-free survival, lower non-relapse mortality and lower relapse incidence. For patients receiving a TCI-low regimen, outcomes are independent on the type of donor. In patients with AML in CR1, older than 50 years and receiving a TCI-intermediate/high conditioning regimen using PTCy, a MUD younger than 40 years is preferable over a MRD older than 50 years.

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INTRODUCTION

The increasing age of patients with hematological malignancies eligible to receive an allogeneic hematopoietic stem cell transplantation (allo-HSCT) has raised the question of whether a human leukocyte antigen (HLA)-matched related donor (MRD) would still be the best donor to use in these circumstances. Indeed, older patients will on average have an older matched sibling as a potential donor with issues such as comorbidities, risk of clonal haematopoiesis of indeterminate potential, and impaired immune and regenerative potential of stem cells [1, 2]. Although donor age is increasingly taken into account in donor selection and a growing number of publications in the field is emerging [3–6], we still lack an unambiguous answer to the question of the role of this risk factor compared to HLA matching and relationship to the patient. Limiting factors for most papers in this field were year of publication, heterogeneity of disease, disease status, and graft-versus-host disease (GvHD) prophylaxis used [7–10]. Indeed, among studies on comparison between an older MRD and a younger matched unrelated donor (MUD) in acute myeloid leukemia (AML), none of them had analysed only patients receiving post-transplant cyclophosphamide (PTCy). For all these reasons we decided to perform a retrospective study among AML patients older than 50 years in first complete remission (CR1) and receiving a graft from an MRD older than 50 years or a MUD younger than 40 years, at EBMT (European Society for Blood and Marrow Transplantation) centers.

METHODS

Study design and data source

This is a retrospective registry-based analysis on behalf of the Acute Leukemia Working Party (ALWP) of the EBMT. The EBMT is a voluntary

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Table 1. Patient and donor characteristics.

	MRD (*n* = 144)	MUD10/10 (*n* = 201)	*p*
Median follow-up [IQR]	27.8 [22.8–31.7]	27.5 [23.6–34.0]	0.67
Patient age in years, median (range)	61.5 (50.7–71.5)	63.1 (50.1–75.8)	0.12
Donor age in years, median (range)	59.4 (50.1–75.2)	27.2 (17.9–40)	<0.0001
Year transplant, median (range)	2019 (2015–2021)	2019 (2015–2021)	0.365
Patient sex			
Male	90 (62.5%)	128 (64%)	0.776
Female	54 (37.5%)	72 (36%)	
Missing	0	1	
Donor/Host combination			
No F/M	67 (46.9%)	145 (72.5%)	<0.0001
F/M	76 (53.1%)	55 (27.5%)	
Missing	1	1	
Karnofsky Performance Status			
<90%	45 (31.9%)	53 (27%)	0.331
≥ 90%	96 (68.1%)	143 (73%)	
Missing	3	5	
HCT-CI			
0	55 (38.2%)	80 (40%)	0.919
1 or 2	40 (27.8%)	52 (26%)	
≥3	49 (34%)	68 (34%)	
Missing	0	1	
Patient CMV			
Negative	31 (21.7%)	43 (21.4%)	0.949
Positive	112 (78.3%)	158 (78.6%)	
Missing	1	0	
Donor CMV			
Negative	41 (29.1%)	99 (49.3%)	0.0002
Positive	100 (70.9%)	102 (50.7%)	
Missing	3	0	
Time diagnosis to HSCT, months, [IQR]	4.4 [3.5–5.4]	5.1 [3.9–6.9]	0.0002
Missing	5	3	
Cytogenetics			
Favorable	2 (1.4%)	6 (3%)	0.056
Intermediate	97 (67.4%)	118 (58.7%)	
Adverse	29 (20.1%)	63 (31.3%)	
Missing	16 (11.1%)	14 (7%)	
Type of AML			
De novo	113 (78.5%)	168 (83.6%)	0.229
Secondary	31 (21.5%)	33 (16.4%)	
Conditioning intensity			
MAC	57 (39.6%)	79 (39.5%)	0.988
RIC	87 (60.4%)	121 (60.5%)	
Missing	0	1	
TCI			
Low [1–2]	53 (36.8%)	91 (45.3%)	0.261
Intermediate [2.5–3.5]	79 (54.9%)	93 (46.3%)	
High [4–6]	12 (8.3%)	17 (8.5%)	
3-drug GvHD prophylaxis			
Yes	55 (38.2%)	120 (59.7%)	<0.001
No	89 (61.8%)	81 (40–3%)	

HCT-CI hematopoietic cell transplantation-specific comorbidity index, *AML* acute myeloid leukemia, *MAC* myeloablative conditioning, *RIC* reduced intensity conditioning, *HSCT* hematopoietic stem cell transplantation, *TCI* transplant conditioning intensity, *CMV* cytomegalovirus, *MRD* matched related donor, *MUD* matched unrelated donor, *IQR* interquartile range, Cytogenetics: good *t*(8;21), inv16 or *t*(16;16); poor monosomy/deletion 5 or 7, abnormalities 11q23, complex karyotype (≥3 abnormalities); intermediate all the others, GvHD graft-versus-host disease.

working group of more than 650 transplantation centers that are required to report all consecutive stem cell transplantations and follow-ups once a year. In the EBMT registry, there is an internal quality control program regarding accuracy and consistency of entered data and audits are regularly performed using queries on missing/incorrect data and follow-up requests. All transplantation centers are required to obtain written informed consent before data registration with the EBMT in accordance with the 1975 Declaration of Helsinki guidelines. The ALWP of the EBMT approved this study.

Patient eligibility

We included all patients older than 50 years with AML in CR1 who underwent a first allo-HSCT from a 10/10 MRD older than 50 years or from a 10/10 MUD younger than 40 years between January 2015 and December 2021, at EBMT centers. Only patients with known type and dosage of drugs used in the conditioning regimen were included. The graft source was non-T-cell depleted peripheral blood stem cells (PBSC) or bone marrow (BM). All patients received PTCy for GvHD prophylaxis. Patients receiving both PTCy and antithymocyte globulin were excluded.

Endpoints and definitions

The primary endpoint was GvHD-free, relapse-free survival (GRFS). Secondary endpoints were relapse incidence (RI), acute and chronic GvHD (aGvHD, cGvHD), non-relapse mortality (NRM), leukemia-free survival (LFS) and overall survival (OS). GRFS was defined as survival without disease relapse and grade 3–4 acute GvHD or extensive chronic GvHD [11]. OS was defined as the time between the date of transplant and death. Relapse was defined as leukemia recurrence at any site. LFS was defined as survival without relapse or progression, and was calculated until the date of first relapse, death from any cause, or the last follow-up. NRM was defined as death from any cause other than relapse. Acute GvHD was graded according to the modified Seattle-Glucksberg criteria [12] and cGvHD according to the revised Seattle criteria [13]. Intensity of conditioning regimens was categorized according to the transplant conditioning intensity (TCI) score and classified as low (TCI ≤ 2), intermediate (TCI 2.5–3.5), or high (TCI 4–6) [14].

Statistical analysis

GRFS, OS, and DFS were estimated by the product-limit method of Kaplan-Meier [15]. Cumulative incidence (CI) functions [16] were used to estimate engraftment, aGvHD, cGvHD, NRM, and RI. Competing risks were as follows: death without engraftment for engraftment; relapse for NRM; death without GvHD for aGvHD and cGvHD, death without relapse for RI. Univariate analysis (UVA) was performed using the log rank test [17] for OS and DFS, and Gray's test [18] for CI function. Variables analysed in the UVA were type of donor (MRD vs. MUD), patient age (median value), female donor to male recipient combination, secondary AML, cytogenetic risk, Karnofsky performance status (KPS), hematopoietic cell transplantation-specific comorbidity index (HCT-CI) [19], TCI, patient and donor cytomegalovirus (CMV) IgG status, time from diagnosis to transplant (median value), year of transplant (median value).

Multivariable analysis (MVA) was performed using the Cox proportional-hazards model [20]. All factors known to influence outcome and factors associated with a univariate analysis *p*-value < 0.10 were first included in

Table 2. Patients and donors characteristics in TCI-low vs. TCI-intermediate/high group.

	TCI [1-2] ($n = 144$)	TCI [2.5–6] ($n = 201$)	*p*
Median follow-up [IQR]	39.87 [32.74–48.28]	23.8 [20.28–26.69]	<0.0001
Patient age in years, median (range)	63.7 (50.1–75.8)	60.9 (50.1–71.6)	<0.0001
Donor age in years, median (range)	33.9 (18–75.2)	36.5 (17.9–70.2)	0.302
Year transplant, median (range)	2018 (2015–2021)	2019 (2015–2021)	<0.0001
Patient sex			
Male	91 (63.2%)	127 (63.5%)	0.954
Female	53 (36.8%)	73 (36.5%)	
missing	0	1	
Donor/Host combination			
No F/M	119 (82.6%)	154 (77%)	0.202
F/M	25 (17.4%)	46 (23%)	
Missing	0	1	
Karnofsky Performance Status			
<90%	53 (37.1%)	45 (23.2%)	0.006
≥90%	90 (62.9%)	149 (76.8%)	
Missing	1	7	
HCT-CI			
0	60 (42%)	75 (37.3%)	0.129
1 or 2	43 (30.1%)	49 (24.4%)	
≥3	40 (28%)	77 (38.3%)	
Missing	1	0	
Patient CMV			
Negative	41 (28.5%)	33 (16.5%)	0.008
Positive	103 (71.5%)	167 (83.5%)	
Missing	0	1	
Donor CMV	70 (49%)	70 (35.2%)	0.011
Negative	73 (51%)	129 (64.8%)	
Positive	1	2	
Missing			
Time diagnosis to HSCT, months, [IQR]	4.6 [3.7–5.9]	4.7 [3.8–6.5]	0.202
Missing	2	6	
Cytogenetics			
Favorable	1 (0.7%)	7 (3.5%)	0.278
Intermediate	93 (64.6%)	122 (60.7%)	
Adverse	40 (27.8%)	52 (25.9%)	
Missing	10 (6.9%)	20 (10%)	
Type of AML			
De novo	116 (80.6%)	165 (82.1%)	0.718
Secondary	28 (19.4%)	36 (17.9%)	
3-drug GvHD prophylaxis			
Yes	55 (38.2%)	121 (60.2%)	<0.001
No	89 (61.8%)	80 (39.8%)	

HCT-CI hematopoietic cell transplantation-specific comorbidity index, *AML* acute myeloid leukemia, *TCI* transplant conditioning intensity, *CMV* cytomegalovirus, *IQR* interquartile range, *HSCT* hematopoietic stem cell transplantation, Cytogenetics: good *t*(8;21), inv16 or *t*(16;16); poor monosomy/deletion 5 or 7, abnormalities 11q23, complex karyotype (≥3 abnormalities); intermediate all the others, GvHD graft-versus-host disease.

Table 3. Univariate analysis of outcomes in the TCI-low and TCI-intermediate/high group, according to type of donor.

		2 years					180 days		2 years	
		Relapse	**NRM**	**LFS**	**OS**	**GRFS**	**Acute GVHD II-IV**	**Acute GVHD III-IV**	**chronic GVHD**	**ext. chronic GVHD**
TCI low	MRD	29% [16.2–43]	14.7% [6.3–26.3]	56.4% [40.5–69.6]	57.6% [41.5–70.8]	40.9% [26.4–54.9]	24.5% [13.5–37.2]	12.2% [4.9–23.1]	36.6% [22.8–50.4]	21.7% [11–34.7]
	MUD10/10	35.7% [25.5–46]	13.2% [6.9–21.5]	51.1% [39.7–61.3]	52.4% [40.8–62.7]	44.4% [33.5–54.8]	27.8% [18.6–37.8]	4.8% [1.6–11]	21.6% [13.2–31.5]	10.7% [4.9–19.1]
	p-value	0.17	0.57	0.32	0.6	0.83	0.68	0.13	0.033	0.06
TCI intermediate/ high	MRD	22.6% [13.8–32.8]	22.6% [13.8–32.8]	54.7% [42.6–65.3]	57.8% [45.4–68.3]	46.1% [34.4–57.1]	23.3% [15–32.8]	7% [2.8–13.8]	44% [32–55.3]	19.1% [11–29]
	MUD10/10	13.9% [7.5–22.2]	4.9% [1.8–10.5]	81.2% [71.2–88]	84.8% [75.5–90.8]	67.2% [55.8–76.2]	15.3% [9.1–22.8]	1.9% [0.4–6.1]	38.5% [28.4–48.6]	15.1% [8–24.3]
	p-value	0.07	0.001	0.001	0.001	0.001	0.18	0.08	0.34	0.29

TCI transplant conditioning intensity, *NRM* non relapse mortality, *LFS* Leukemia free survival, *OS* overall survival, *GvHD* graft-versus-host disease, GRFS GvHD-free, relapse-free survival.

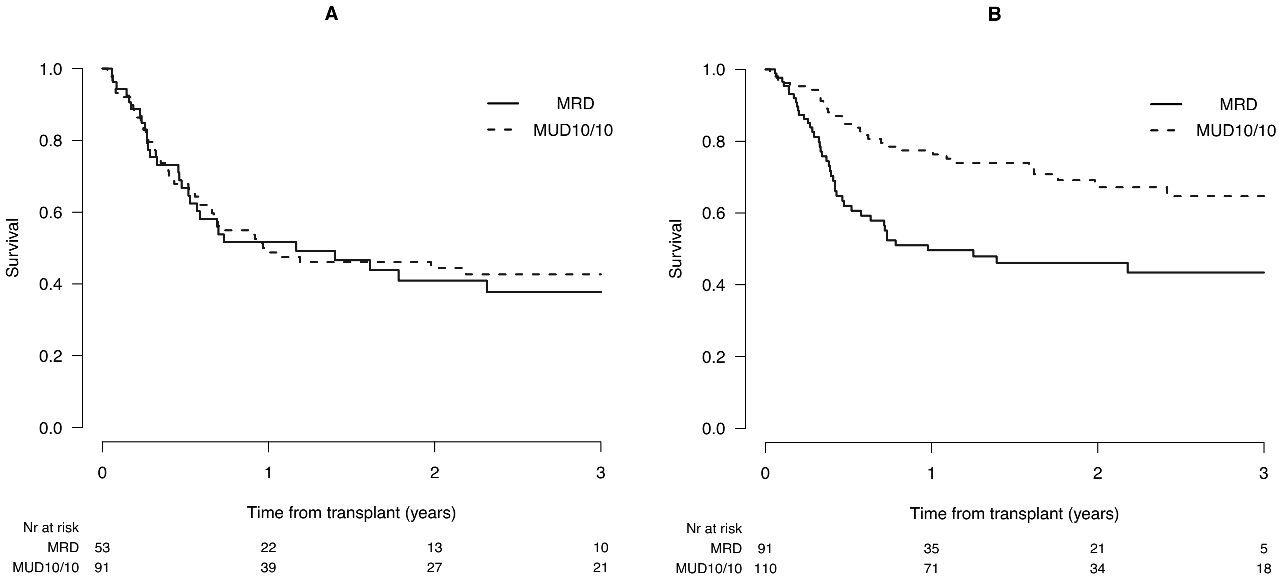

Fig. 1 GRFS according to donor type and intensity of conditioning regimen. GRFS according to donor type in TCI-score low **A** and in TCI-score intermediate/high **B**.

the model. Then, a stepwise backward procedure was used with a cut-off significance level of 0.10 for deleting factors from the model. The type I error rate was fixed at 0.05 for determination of associated factors. As a strong interaction was observed between TCI score and type of donor, we compared transplant outcomes between MRD and MUD separately for TCI-low and TCI-intermediate/high recipients. Analyses were performed using R statistical software version 4.2.3 (R Development Core Team, Vienna, Austria).

RESULTS

Patient and donor characteristics

A total of 410 patients fulfilled the inclusion criteria except for the conditioning regimen details. For 345 out of 410 (84%) patients all the inclusion criteria were met and therefore these patients were included in the analysis. Patient and donor characteristics are shown in Table 1. Of note, patients receiving a graft from a MRD older than 50 years compared to patients receiving one from a MUD younger than 40 years received the transplant earlier, their donors were more often CMV IgG positive and in that group a higher proportion of male patients received the transplant from a female donor. No differences were found with respect to year of transplant, KPS, HCT-CI and TCI. Differences in patient characteristics in the TCI-low vs. TCI intermediate/high group are shown in Table 2. Graft-versus-host disease prophylaxis with a three-drug combination regimen was offered to 55 of 144 (38.2%) patients who received TCI-low and to 121 of 201 (60.2%) patients who received TCI-intermediate/high conditioning regimen (Table 2). The three-drug approach was more popular in recent years. The most often used associations (in addition to PTCy) were as follows: cyclosporine plus mycophenolate mofetil (MMF), tacrolimus plus MMF or rapamycine plus MMF.

Transplant outcomes

The 2-year results of the UVA according to type of donor in the TCI-low and TCI-intermediate/high groups are shown in Table 3.

In the TCI-low group, the only difference in transplant outcomes between older MRD and younger MUD was in overall incidence of cGvHD which was lower for patients receiving a graft from a younger MUD 21.6% [95% CI: 13.2–31.5] vs. 36.6% [95% CI: 22.8–50.4] ($p = 0.033$). In the TCI-intermediate/high group, 2-year NRM, LFS, OS and GRFS were all in favor of patients receiving a graft from a younger MUD.

The 2-year GRFS for patients with a younger MUD vs. an older MRD was 44.4% [95% CI: 33.5–54.8] vs. 40.9% [95% CI: 26.4–54.9] in the TCI-low group ($p = 0.83$) (Fig. 1A) while it was 67.2% [95% CI: 55.8–76.2] vs. 46.1% [95% CI: 34.4–57.1] in the TCI-intermediate/high group ($p = 0.001$) (Fig. 1B).

On MVA (Table 4), donor type was not a risk factor for any of the transplant outcomes in the TCI-low group (Table 4) while in the TCI-intermediate/high group, patients receiving a graft from a younger MUD had a significantly better GRFS, LFS, OS, RI and NRM but no difference in terms of acute or cGvHD (Table 4).

DISCUSSION

Over the past 25 years, the landscape of allo-HSCT has changed from being rarely performed in patients aged 50 years or older to accounting for a little less than half of the transplantations reported in the USA and Europe [21]. As the age of MRD increases, several studies have attempted to answer the question of whether a younger MUD could have been of benefit compared to an older MRD [7–10].

In our study we analysed patients aged over 50 years with AML in CR1 having received PTCy as the back-bone for GvHD prevention in the context of an HLA-matched donor donating PBSC. Indeed, the use of PTCy for GvHD prophylaxis outside the haploidentical transplant setting is increasing both in the USA [22] and Europe [23, 24] with improved results compared to standard drug combinations [25].

Of note, a comparison between the two types of HLA-matched donors (older MRD versus younger MUD), was conducted separately for patients receiving a TCI-low conditioning regimen or a TCI-intermediate/high regimen. Indeed, TCI has already resulted in providing a better assessment of NRM and relapse risk, a finer categorization and a better discriminating ability compared with the reduced intensity conditioning (RIC)/myeloablative conditioning (MAC) approach, and it accounts for new regimens that were not readily amenable to the RIC/MAC definition [14, 26] but widely used in our centers.

The choice of a similar GvHD platform could have contributed to explaining the absence of any difference in terms of GvHD incidence according to donor type in both TCI groups, in contrast with the findings of the first large study in this field from the CIBMTR (Center for International Blood and Marrow Transplant

Table 4. MVA of outcomes in the TCI-low and TCI-intermediate/high group.

TCI low	RELAPSE		NRM		LFS		OS		GRFS		Acute GVHD II-IV		chronic GVHD	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
MUD 10/10 vs. MRD	**1.24 (0.61–2.51)**	**0.56**	**1.19 (0.4–3.55)**	**0.76**	**1.26 (0.7–2.29)**	**0.44**	**1.07 (0.59–1.94)**	**0.83**	**0.98 (0.57–1.69)**	**0.95**	**1.2 (0.53–2.71)**	**0.66**	**0.77 (0.34–1.72)**	**0.52**
Age (per 10 y)	0.77 (0.47–1.26)	0.29	0.94 (0.4–2.22)	0.9	0.81 (0.53–1.25)	0.34	0.84 (0.54–1.3)	0.42	0.84 (0.57–1.25)	0.39	1.31 (0.69–2.47)	0.41	0.83 (0.44–1.56)	0.57
Adverse cytogenetics	2.16 (1.12–4.17)	0.022	1.46 (0.55–3.9)	0.45	1.87 (1.09–3.2)	0.023	1.93 (1.12–3.31)	0.018	1.4 (0.85–2.32)	0.18	0.37 (0.14–0.98)	0.045	0.55 (0.22–1.39)	0.21
Time diagnosis to HSCT (months)	1 (0.89–1.14)	0.94	1.09 (0.96–1.24)	0.2	1.03 (0.95–1.13)	0.47	1.05 (0.97–1.15)	0.24	1.01 (0.93–1.09)	0.9	0.99 (0.87–1.12)	0.84	0.77 (0.57–1.03)	0.083
Year of HSCT	1.09 (0.92–1.3)	0.32	0.94 (0.71–1.23)	0.63	1.04 (0.9–1.2)	0.6	1 (0.86–1.16)	0.99	0.98 (0.86–1.11)	0.7	1.06 (0.88–1.27)	0.55	0.88 (0.72–1.08)	0.22
female to male	0.33 (0.1–1.14)	0.081	3.13 (1.07–9.18)	0.038	0.97 (0.47–2.02)	0.94	0.86 (0.4–1.84)	0.69	1.35 (0.72–2.54)	0.35	1.14 (0.42–3.06)	0.8	1.29 (0.5–3.31)	0.59
KPS > 90%	1.94 (0.98–3.83)	0.058	0.8 (0.3–2.12)	0.65	1.44 (0.83–2.49)	0.19	1.47 (0.84–2.58)	0.18	1.45 (0.87–2.4)	0.15	0.84 (0.42–1.69)	0.63	0.84 (0.4–1.75)	0.65
other versus CMV D-/R-	1.26 (0.61–2.59)	0.54	1.16 (0.38–3.59)	0.79	1.23 (0.67–2.25)	0.51	1.34 (0.71–2.51)	0.37	0.78 (0.46–1.33)	0.36	1.03 (0.48–2.22)	0.94	0.76 (0.34–1.67)	0.49

TCI intermediate/ high	RELAPSE		NRM		LFS		OS		GRFS		Acute GVHD II-IV		chronic GVHD	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
MUD 10/10 vs. MRD	**0.32 (0.14-0.73)**	**0.007**	**0.19 (0.07–0.55)**	**0.002**	**0.27 (0.14–0.5)**	**<0.0001**	**0.29 (0.15–0.55)**	**0.0002**	**0.41 (0.24–0.7)**	**0.001**	**0.59 (0.29–1.21)**	**0.15**	**0.65 (0.38–1.12)**	**0.12**
Age (per 10 y)	1.32 (0.63–2.79)	0.46	1.85 (0.73–4.68)	0.19	1.52 (0.85–2.71)	0.16	1.66 (0.89–3.08)	0.11	1.4 (0.86–2.29)	0.18	0.74 (0.39–1.39)	0.35	0.87 (0.54–1.41)	0.58
Adverse cytogenetics	3.3 (1.42–7.68)	0.005	1.24 (0.38–4.07)	0.72	2.32 (1.19–4.54)	0.014	2.41 (1.19–4.85)	0.014	1.79 (0.98–3.3)	0.06	3.12 (1.49–6.53)	0.003	0.9 (0.45–1.78)	0.76
Time diagnosis to HSCT (months)	1.01 (0.9–1.13)	0.85	1.06 (0.95–1.17)	0.29	1.03 (0.96–1.11)	0.4	1.02 (0.95–1.1)	0.61	1.02 (0.96–1.09)	0.52	0.94 (0.81–1.08)	0.35	1.02 (0.95–1.1)	0.63
Year of HSCT	0.75 (0.57–0.99)	0.043	0.77 (0.57–1.03)	0.077	0.76 (0.62–0.93)	0.008	0.8 (0.65–0.98)	0.031	0.78 (0.66–0.92)	0.003	0.96 (0.77–1.21)	0.76	0.93 (0.78–1.11)	0.42
female to male	1.1 (0.45–2.65)	0.84	1.51 (0.58–3.94)	0.4	1.27 (0.67–2.42)	0.47	1.16 (0.58–2.3)	0.67	1.34 (0.77–2.35)	0.3	1.02 (0.47–2.25)	0.95	1.07 (0.56–2.05)	0.83
KPS > 90%	0.97 (0.41–2.3)	0.95	1.03 (0.35–3.05)	0.95	1 (0.51–1.95)	0.99	1.26 (0.6–2.66)	0.54	1.07 (0.58–1.95)	0.83	0.93 (0.43–2.01)	0.85	1.28 (0.68–2.41)	0.45
other versus CMV D-/R-	NA	1	1.05 (0.21–5.2)	0.95	2.45 (0.55–10.87)	0.24	1.77 (0.4–7.93)	0.46	1.36 (0.51–3.64)	0.54	0.61 (0.19–1.93)	0.4	0.78 (0.33–1.84)	0.57

TCI transplant conditioning intensity, *NRM* non relapse mortality, *LFS* Leukemia free survival, *OS* overall survival, *GvHD* graft-versus-host disease, *GRFS* GvHD-free, relapse-free survival, *MUD* matched unrelated donor, *MRD* matched related donor, Cytogenetics: good t(8;21), inv16 or t(16;16); poor monosomy/deletion 5 or 7, abnormalities 11q23, complex karyotype (≥ 3 abnormalities); intermediate all the others, *HCT* hematopoietic cell transplantation, *KPS* Karnofsky performance status, *CMV* cytomegalovirus.

Research) that in 2013 demonstrated an improved OS and reduced GvHD incidence for MRD over 50 years versus younger MUD, in patients with acute leukemia and lymphoma [7] and in contrast with even more recent studies on patients with myelodysplastic syndromes [9] and AML [10].

Patients in the TCI-intermediate/high group had a lower RI and a higher LFS if transplanted from a MUD younger than 40 years in line with the results of a more recent study from the CIBMTR analysing transplants performed from 2011 and 2018 in AML patients aged 50 years or more, receiving a graft from an MRD ≥ 50 years or from an MUD ≤ 35 years [10] and in line with a similar study in B-cell acute lymphoblastic leukemia [27], and MDS patients [9].

Patients in the TCI-intermediate/high group also showed a lower NRM when receiving the transplant from a younger MUD in contrast with Murthy [9] and Abid [10] who described a higher NRM in younger MUD, but in line with the contemporary literature about impact of donor age on NRM regardless of HLA-matching [6, 28, 29].

A lower RI and a lower NRM translated into a higher OS, LFS and GRFS in patients with a MUD younger than 40 years in the TCI-intermediate/high group.

Conversely to what was found for the TCI-intermediate/high group, but similar to the results of a previous EBMT study on patients with AML in CR1 receiving grafts from an older MRD or a younger MUD after a RIC regimen [8], we didn't find any difference in transplant outcomes between patients receiving grafts from a MRD older than 50 years or a MUD younger than 40 years in the TCI-low group.

With the limitations of a retrospective study but with the strengths of homogeneous patients in terms of disease, disease status, patient age, GvHD prophylaxis, and intensity of conditioning regimens, we can conclude that the choice of a MRD older than 50 years or a MUD younger than 40 years does not impact transplant outcomes if using a TCI-low conditioning regimen. On the contrary, in the setting of intermediate or high TCI regimens, a younger MUD improves all transplant outcomes except for GvHD incidence.

DATA AVAILABILITY

The dataset supporting the conclusions of this article is available from the ALWP of the EBMT at the Saint Antoine Hospital, Paris.

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AUTHOR CONTRIBUTIONS

SP, ML, MM, JS and FC: designed the study. ML: performed statistical analysis and helped with the interpretation of the results. SP: wrote the manuscript. GC, AECB, JP,

EM, GVG, MR, MJPC, SS, JV, AK, AB, JS, FC: provided patients for the study. All authors reviewed and approved the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The scientific board of the ALWP of the EBMT approved this study. All patients gave written informed consent for the use of their data.

CONSENT FOR PUBLICATION

Not applicable for individual patient data. This is a pooled analysis.

ADDITIONAL INFORMATION

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