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ARTICLE

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Allogeneic hematopoietic cell transplantation for patients with AML aged 70 years or older in first remission. A study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT)

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Accessibility to allogeneic hematopoietic cell transplantation (HCT) programs for older patients is growing constantly. We report on the clinical outcomes of a group of 701 adults aged ≥70 years, with acute myeloid leukemia (AML) in first complete remission (CR1), who received a first HCT, from HLA-matched sibling donors (MSD), 10/10 HLA-matched unrelated donors (UD), 9/10 HLA-mismatched unrelated donors (mUD) or haploidentical (Haplo) donors. The 2-year overall survival (OS) was 48.1%, leukemia-free survival (LFS) 45.3%, relapse incidence (RI) 25.2%, non-relapse mortality (NRM) 29.5% and GVHD-free, relapse-free survival (GRFS), 33.4%. Compared to MSD, patients transplanted from Haplo and UD presented lower RI (HR 0.46, 95% CI 0.25–0.8, $p = 0.02$ and HR 0.44, 95% CI: 0.28–0.69, $p = 0.001$, respectively); this translated into prolonged LFS for Haplo (HR 0.62, 95% CI: 0.39–0.99, $p = 0.04$). Patients transplanted from mUD exhibited the highest NRM incidence (HR 2.33, 95% CI: 1.26–4.31, $p = 0.007$). HCT in selected adult CR1 AML patients >70 years is feasible and could be associated with good clinical outcomes. Prospective clinical trials are warranted.

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INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) has curative potential for hematologic malignancies in different phases of their treatment algorithm. Acute myeloid leukemia (AML) is the most frequent indication for allogeneic HCT [1, 2]. Considering that the median age at diagnosis of AML is 68 years, the majority of HCT candidates are elderly patients. Several studies have shown that age alone does not absolutely contraindicate allogeneic HCT [3–6]. According to the Center for International Blood and Marrow Transplant Research (CIBMTR), the number of patients ≥65 years who received allogeneic HCT doubled from 10% in 2000–2006 to 22% in 2007–2013, respectively. Notably, in 2017, 31% of allogeneic HCT recipients were aged ≥60 while approximately 6% were at least 70 years old [7]. In Europe, based on the European Society of Blood and Marrow Transplantation (EBMT) registry data, there is also a clear trend towards a wider application of HCT among patients in their eighth decade: the absolute number of allogeneic HCT recipients rose from only 40 during 2000–2004 to 256 in 2005–2009 and from 1005 in 2010–2014 to 2083 in 2015–2019 [1]. The increase in median age of HCT recipients has unavoidably brought several unsolved clinical issues regarding many aspects of the complex allogeneic HCT procedure. Aside from establishing HCT indications by risk category and correct timing, one of the most relevant aspects of

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this pathway is the identification of a suitable hematopoietic cell donor for older adult patients. A related HLA-matched sibling (MSD) still represents the first choice in donor, but quite often, major comorbidities limit their applicability; adult 10/10 human leukocyte antigen (HLA)-matched unrelated donors (UD) are the first-alternative choice, but their availability is limited. As graft-versus-host disease (GVHD) risks are historically, quite high after mismatched UD (mUD) HCT, there is comprehensible reluctance in proceeding to transplantation when an HLA-matched UD is not available, especially among older recipients [8]. Older transplant candidates who lack HLA-MSD or a suitable UD, may have HLA-mismatched siblings, of similar age, but most of them have offspring, who are 20–40 years younger. HLA-half matched related donors are increasingly used worldwide, mostly due to the adoption of T-cell replete haploidentical (Haplo) transplants [9]. Comparative studies examining clinical outcomes across different donor types for older adults with AML are lacking. Our goal is to describe clinical outcomes after allogeneic HCT among older AML patients, aged ≥70 years, in first complete remission (CR1), according to donor type.

METHODS

Patients

This is a multicenter, retrospective registry-based analysis, approved by the Acute Leukemia Working Party (AWLP) of the EBMT. The EBMT is a voluntary group that represents more than 600 transplant centers, mostly from European countries. EBMT centers pay annual subscriptions to maintain the registry. Since 1990, patients have provided informed consent authorizing the use of their personal information for research purposes. The study was approved by the ALWP of the EBMT Institutional Review Board and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The validation and quality control program includes verification of computer read-out of the data, cross-check with national registries and on-site visits by selected teams. The present study analyzes the outcomes of adult patients ≥70 years, affected by AML in CR1 who had received an allogeneic HCT from 2000 to 2019, from HLA-MSD ($n = 114$), HLA 10/10 matched unrelated donors (UD) ($n = 407$), HLA 9/10 matched unrelated (mUD) donors ($n = 85$) and Haplo donors ($n = 95$). Cell source was either peripheral blood stem cells (PBSC) or bone marrow. Only patients receiving a first allogeneic HCT were included. Ex-vivo T-cell depleted transplants were not included in the study.

Endpoints (and definitions)

The objective of the study was to analyze the clinical outcomes and transplant related mortality after allogeneic HCT in patients with AML in CR1, aged ≥70 years, both in the overall study population and in four different subgroups according to the type of donor. Leukemia-free survival (LFS) was defined as the time from transplantation to relapse or death from any cause, and overall survival (OS) was defined as the time from transplantation to death from any cause [10]. Relapse incidence (RI) was defined as disease recurrence documented by blast reappearance (>5%) on peripheral blood or marrow smears, or extramedullary localization by radiographic means. Non-relapse mortality (NRM) was defined as death while in continuous remission. Grading of GVHD was based on consensus criteria [11]. Chronic GVHD was defined clinically by the treating physician utilizing standard criteria [12]. GVHD-free/relapse-free survival (GRFS) was defined as survival free of events including grades III-IV acute GVHD, extensive chronic GVHD, relapse, or death [13]. Reduced intensity conditioning (RIC) was defined as regimens combining fludarabine with either <6 Gy total body irradiation (TBI), ≤8 mg/kg busulfan, or ≤140 mg/m^2 melphalan or with other nonmyeloablative drugs as previously reported [14]. Cytogenetic risk was stratified using the MRC-UK classification, as previously reported [15].

Statistical methods

Probabilities of OS, LFS, and GRFS were calculated using the Kaplan–Meier method. Cumulative incidence was used to estimate the endpoints of NRM, RI, acute and chronic GVHD to accommodate competing risks. Relapse and death were considered as competing risks to assess acute and chronic GVHD incidence. Univariate analyses were carried out using Gray's test for cumulative incidence functions and the log-rank test for OS, GRFS, and LFS. A Cox proportional-hazards model was used for multivariable regression. All variables differing significantly across the groups, and factors known to influence outcomes were included in the Cox model and were type of donors, time from diagnosis to HCT, age at transplant, year of transplant, Female to male donor status, CMV status for patients and donors, regimen intensity, cytogenetics, secondary AML status and Karnofsky performance status (KPS). Results were expressed as the hazard ratio (HR) with the 95% confidence interval (95% CI). All p-values were two-sided with a type 1 error rate fixed at 0.05. Statistical analyses were performed with R 3.4.1 [R Core Team (2017). R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria] software packages.

RESULTS

Table 1 shows the characteristics of the study population. A total of 701 patients with a median age of 71.6 (range 70–80) years were included in the analysis. Donors were MSD ($n = 114$), 10/10 HLA-matched UD ($n = 407$), 9/10 mUD ($n = 85$) and Haplo ($n = 95$). Cytogenetics was classified as intermediate-risk in 51%, adverse-risk in 14%, favorable risk in 8% (cytogenetics was not available/failed for 237 patients). Two hundred ten (30%) patients had secondary AML. A total of 102 (15%) patients received a myeloablative conditioning (MAC) regimen and 588 (85%) a reduced intensity conditioning (RIC) regimen. Male patients transplanted from MSD more frequently received grafts from female donors ($p < 0.01$). Recipients of Haplo donors more frequently presented adverse-risk cytogenetics, received marrow grafts ($p < 0.001$) and total body irradiation (TBI)-based conditioning regimens. In vivo, T-cell depletion was performed in 382 (56%) of the transplants and included: anti-thymocyte globuline (ATG) in 44%, Campath in 10% and ATG plus Campath in 1%. Post-transplant cyclophosphamide (PT-CY) for GVHD prophylaxis was used in 116 (17%) patients (of which 79 were recipients of Haplo donors). Most patients received busulfan-based ($n = 275$, 39.3%) and low-dose TBI-based ($n = 211$, 30.3%) regimens. Only three patients received myeloablative TBI.

With a median follow-up of 2.9 years, the overall 2-year rate of OS was 48.1% (95% CI: 44.1–52.1), LFS was 45.3% (95% CI: 41.3–49.2), RI was 25.2% (95% CI: 21.9–28.7), NRM was 29.5% (95% CI: 26–33.1) and GRFS was 33.4% (95% CI: 29.5–37.3). Global incidence of grade III-IV acute GVHD at day-100 was 7.6% (95% CI: 5.8–9.8), while 2-year extensive chronic GVHD incidence was 18.2% (95% CI: 15.1–21.5) (Table 2). Engraftment rate was 96% overall.

Overall survival and leukemia-free survival

The univariate analysis showed two-year OS: 54.1% (95% CI: 41.6–65) for Haplo donors, 52.5% (95% CI: 47.1–57.5) for 10/10 HLA-matched UD, 39% (95% CI: 29.1–48.8) for MSD and 33.7% (95% CI: 23.3–44.4) for mUD ($p = 0.001$). Similarly, 2-year LFS showed a positive trend for recipients of half-matched family donors: 55.8% (95% CI: 43.5–66.4) for Haplo, 48.1% (95% CI: 42.8–53.2) for 10/10 UD, 36.7% (95% CI: 27.2–46.2) for MSD and 33.2% (95% CI: 22.9–43.8) for mUD ($p = 0.001$) (Fig. 1 and Table 2). The better outcomes described for Haplo were confirmed in the multivariate analysis (MVA). Recipients of Haplo grafts experienced an extended LFS (HR 0.62, 95% CI: 0.39–0.99, $p = 0.04$) and lower RI (HR 0.46, 95% CI: 0.25–0.87, $p = 0.02$). No other variables tested were significantly associated with OS or LFS. Other prognostic factors as per MVA were the combination of female recipient of male donor, which adversely influenced both OS (HR1.64, 95% CI: 1.21–2.22, $p = 0.001$) and LFS (HR 1.47, 95% CI: 1.1–1.98, $p = 0.01$); as did a poor KPS (<90) on OS: HR 0.75, 95% CI: 0.58–0.97, $p = 0.03$) and LFS (HR 0.76, 95% CI: 0.59–0.97, $p = 0.03$). Poor risk cytogenetics predicted inferior OS (HR 1.47, 95% CI: 1.05–2.04, $p = 0.02$) (Table 3).

Table 1. Study population characteristics.

Variables	Modalities	Total (*N* = 701)	Haplo (*N* = 95)	MSD (*N* = 114)	UD (*N* = 407)	mUD (*N* = 85)	Test *p*-value
Age patients	median (range)	71.6 (70–80.4)	72 (70–78.7)	71.5 (70–76)	71.6 (70–79.6)	71.5 (70–80.4)	0.8606
Year of HCT	median (range)	2016 (2002–2019)	2018 (2008–2019)	2014 (2002–2019)	2016 (2007–2019)	2015 (2008–2019)	<0.0001
Diagnosis to HCT	median (range)	4.83 (1.3–30.4)	4.9 (1.3–29.9) [3.6–6.4]	4.5 (1.7–22.3) [3.4–5.6]	4.8 (1.4–30.4) [3.6–6.3]	5.4 (1.3–26.6) [4.1–7.1]	0.0308
Sex donor	Female *n* (%)	205 (29.7)	30 (31.6)	62 (54.4)	82 (20.6)	31 (37.8)	<0.0001
	Male	485 (70.3)	65 (68.4)	52 (45.6)	317 (79.4)	51 (62.2)	
	missing	11	0	0	8	3	
Female donor to male recipient	No	583 (84.1)	74 (77.9)	79 (69.3)	365 (91)	65 (78.3)	<0.0001
	Yes	110 (15.9)	21 (22.1)	35 (30.7)	36 (9)	18 (21.7)	
	missing	8	0	0	6	2	
CMV Patient	Negative	208 (30.1)	18 (18.9)	30 (27.5)	132 (32.8)	28 (32.9)	0.0523
	Positive	483 (69.9)	77 (81.1)	79 (72.5)	270 (67.2)	57 (67.1)	
	missing	10	0	5	5	0	
CMV donor	Negative	340 (49.3)	42 (44.7)	40 (37)	206 (51.1)	52 (61.9)	0.0043
	Positive	349 (50.7)	52 (55.3)	68 (63)	197 (48.9)	32 (38.1)	
	missing	12	1	6	4	1	
Secondary AML	No	491 (70)	67 (70.5)	87 (76.3)	279 (68.6)	58 (68.2)	0.438
	Yes	210 (30)	28 (29.5)	27 (23.7)	128 (31.4)	27 (31.8)	
Cytogenetics	favorable	8 (1.1)	0 (0)	0 (0)	6 (1.5)	2 (2.4)	
	interm	358 (51.1)	55 (57.9)	61 (53.5)	209 (51.4)	33 (38.8)	
	NA/failed	237 (33.8)	22 (23.2)	39 (34.2)	145 (35.6)	31 (36.5)	0.362
	adverse	98 (14)	18 (18.9)	14 (12.3)	47 (11.5)	19 (22.4)	
Karnofsky	<90	193 (29.8)	28 (31.1)	30 (29.7)	115 (30.6)	20 (25)	0.7854
	≥90	454 (70.2)	62 (68.9)	71 (70.3)	261 (69.4)	60 (75)	
	missing	54	5	13	31	5	
HCT-CI	0	217 (45.5)	32 (53.3)	124 (44.1)	26 (42.6)	35 (46.7)	0.2735
	1–2	123 (25.8)	15 (25)	81 (28.8)	12 (19.7)	15 (20)	
	≥3	137 (28.7)	13 (21.7)	76 (27)	23 (37.7)	25 (33.3)	
	missing	224	54	126	24	20	
Cell source	BM	43 (6.1)	20 (21.1)	4 (3.5)	17 (4.2)	2 (2.4)	<0.0001
	PB	658 (93.9)	75 (78.9)	110 (96.5)	390 (95.8)	83 (97.6)	
TBI	No	488 (69.8)	50 (53.8)	84 (73.7)	298 (73.2)	56 (65.9)	0.0018
	Yes	211 (30.2)	43 (46.2)	30 (26.3)	109 (26.8)	29 (34.1)	
	missing	2	2	0	0	0	
Myeloablative regimen	No	588 (85.2)	81 (89)	99 (86.8)	333 (83)	75 (89.3)	0.2738
	Yes	102 (14.8)	10 (11)	15 (13.2)	68 (17)	9 (10.7)	
	missing	11	4	0	6	1	
In vivo T cell depletion	No	302 (44.2)	83 (94.3)	56 (53.3)	131 (32.3)	32 (37.6)	<0.0001
	Yes	382 (55.8)	5 (5.7)	49 (46.7)	275 (67.7)	53 (62.4)	
	missing	17	7	9	1	0	
PT-CY	No	565 (83)	9 (10.2)	101 (96.2)	385 (95.3)	70 (83.3)	<0.0001
	Yes	116 (17)	79 (89.8)	4 (3.8)	19 (4.7)	14 (16.7)	
	missing	20	7	9	3	1	

CI confidence interval, *MSD* matched sibling donor, *UD* unrelated donor, *mUD* mismatched unrelated donor, *HCT* allogeneic hematopoietic cell transplantation, *CMV* cytomegalovirus, *BM* bone marrow, *PB* peripheral blood, *TBI* total body irradiation, *PT-CY* post-transplant cyclophosphamide.

Disease relapse

Univariate RI at 2-year was 21.9% (95% CI: 17.9–26.3) for 10/10 HLA-matched UD, 22% (95% CI: 13.2–32.1) for Haplo, 25.2% (95% CI: 16.1–35.3) for mUD, and 39.8% (95% CI: 30.1–49.3) for MSD (Fig. 1). In MVA both recipients of 10/10 UD (HR 0.44, 95% CI: 0.28–0.69, $p = 0.001$) and Haplo (HR 0.46, 95% CI: 0.25–0.87, $p = 0.02$) had a lower risk of RI compared to recipients of MSD grafts (Table 3).

Table 2. Clinical outcomes for the total population and according to donor type.

	Total			MSD			Haplo			UD			mUD		
	N	Event (*N*)	(95% CI)	*N*	Event (*N*)	(95% CI)	*N*	Event (*N*)	(95% CI)	*N*	Event (*N*)	(95% CI)	*N*	Event (*N*)	(95% CI)
Median FU (y)	701		2.9 (2.6–3.1)	114		3.5 (1.9–4.5)	95		2 (1.5–2.7)	407		3 (2.6–3.1)	85		3.4 (2.2–4.1)
OS (2 y)	701	322	48.1 (44.1–52.1)	114	61	39 (29.1–48.8)	95	35	54.1 (41.6–65)	407	174	52.5 (47.1–57.5)	85	52	33.7 (23.3–44.4)
LFS (2 y)	700	347	45.3 (41.3–49.2)	114	66	36.7 (27.2–46.2)	95	35	55.8 (43.5–66.4)	406	193	48.1 (42.8–53.2)	85	53	33.2 (22.9–43.8)
GRFS (2 y)	655	401	33.4 (29.5–37.3)	100	74	20.3 (12.5–29.4)	92	41	47.2 (35.1–58.3)	386	226	36.8 (31.8–41.9)	77	60	19 (10.8–28.9)
RI (2 y)	700	160	25.2 (21.9–28.7)	114	41	39.8 (30.1–49.3)	95	17	22 (13.2–32.1)	406	82	21.9 (17.9–26.3)	85	20	25.2 (16.1–35.3)
NRM (2 y)	700	187	29.5 (26–33.1)	114	25	23.5 (15.8–32)	95	18	22.2 (13.6–32.2)	406	111	30 (25.3–34.7)	85	33	41.6 (30.5–52.3)
aGVHD-II/IV (100 d)	635	129	20.4 (17.4–23.6)	103	19	18.5 (11.6–26.5)	90	26	29.1 (20–38.7)	367	66	18.1 (14.3–22.2)	75	18	24 (15–34.2)
aGVHD-III/IV (100 d)	658	50	7.6 (5.8–9.8)	103	8	7.8 (3.6–14)	91	5	5.5 (2–11.6)	384	26	6.8 (4.6–9.6)	80	11	13.7 (7.3–22.3)
CGVHD (2 y)	651	209	36.1 (32.2–40)	102	33	36.3 (26.4–46.3)	93	22	31.7 (20.9–43.1)	380	133	38.3 (33.2–43.4)	76	21	29.5 (19.2–40.5)
CGVHD Ext (2 y)	643	103	18.2 (15.1–21.5)	100	17	19 (11.6–27.9)	91	6	8.9 (3.5–17.3)	376	64	18.9 (14.9–23.3)	76	16	22.7 (13.6–33.1)

CI confidence interval, *MSD* matched sibling donor, *UD* unrelated donor, *mUD* mismatched unrelated donor, a*GVHD* acute graft-versus-host disease, *CGVHD* chronic graft-versus-host disease, *NRM* non-relapse mortality, *LFS* leukemia-free survival, *OS*, overall survival, *RI* relapse incidence, GRFS graft-versus-host disease/relapse-free survival, *d* days, *y* years.

Non-relapse mortality

Table 2 shows that recipients of 9/10 HLA-mUD showed the highest rates of transplant-related toxicity, with 2-year cumulative incidence of NRM of 41.6% (95% CI: 30.5–52.3); followed by 10/10 HLA-matched UD with 30% (95% CI: 25.3–34.7), respect to MSD, with 23.5% (95% CI: 15.8–32) and Haplo, with 22.2% (95% CI: 13.6–32.2). Transplantation from a mUD maintained its association with higher NRM rates (HR 2.33, 95% CI: 1.26–4.31, $p = 0.007$) in the multivariate model. Moreover, the combination of female donor/male recipient (HR 1.94, 95% CI: 1.32–2.86, $p = 0.001$), the use of MAC (HR 1.54, 95% CI: 1.01–2.35, $p = 0.04$) and recipient CMV seropositivity (HR 1.5, 95% CI: 1.01–2.22, $p = 0.04$) were all associated with higher rates of toxicity (Table 3).

GVHD and GRFS

The incidence of grades II/IV acute GVHD at day-100 were 29.1% (95% CI: 20–38.7%) for recipients of Haplo donors, 24% (95% CI: 15–34.2%) for mUD, and 18.5% (95% CI: 11.6–26.5%) for MSD and 18.1% (95% CI: 14.3–22.2%) for 10/10 UD, respectively ($p = 0.03$). Corresponding day-100 incidence of grades III/IV acute GVHD were 13.7% (95% CI: 7.3–22.3%) for HLA 9/10 mUD, 7.8% (95% CI: 3.6–14%) for MSD, 6.8% (95% CI: 4.6–9.6%) for 10/10 UD and 5.5% (95% CI: 2–11.6%) for recipients of Haplo, respectively ($p = 0.13$) (Fig. 2a). In univariate analysis, conditioning regimens not including TBI (9.2% vs 4.1%, $p = 0.05$) and recipients of in vivo T-cell depletion (9.3% vs. 5.4%, $p = 0.06$) showed a trend towards higher rates of grades III/IV acute GVHD, not confirmed in the multivariate model. Two-year incidence of chronic GVHD was 38.3% (95% CI: 33.2–43.4%) for 10/10 UD, 36.3% (95% CI: 26.4–46.3%) for MSD, 31.7% (95% CI: 20.9–43.1%) for Haplo and 29.5% (95% CI: 19.2–40.5%) for 9/10 HLA-mUD, respectively ($p = 0.33$). Extended chronic GVHD rates were highest for 9/10 HLA-mUD with 22.7% (95% CI: 13.6–33.1%), followed by MSD with 19% (95% CI: 11.6–27.9%), 18.9% for 10/10 UD (95% CI: 14.9–23.3%), and 8.9% for recipients of Haplo grafts (95% CI: 3.5–17.3), respectively ($p = 0.15$) (Fig. 2b). In MVA, the donor type did not show a significant influence on Acute or Chronic GvHD. GRFS at 2-year was 33.4% (95% CI: 29.5–37.3) (Fig. 3); The univariate analysis showed 2-year GRFS of 20.3% (95% CI: 12.5–29.4%) for MSD, 47.2% (95% CI: 35.1–58.3%) for Haplo, 36.8% (95% CI: 31.8–41.9%) for 10/10 HLA-matched UD and 19% (95% CI: 10.8–28.9%) for mUD.

DISCUSSION

The search for the ideal donor for HCT in older adults with AML in CR1 remains a matter of debate. Our study showed clinical outcomes after allogeneic HCT in a homogeneous cohort of 701 older adult AML patients, aged ≥70 years. The first informative data is that estimated OS for older HCT recipients in the first two decades since 2000 is improving, attesting to 48.1% at 2 years, compared with the survival in a previously reported EBMT study. The analysis showed that, among 713 patients aged ≥69 years, the probability of survival at 2 years was 38%, a clear step up from the past where there was a dismal 2-year OS of 26% for patients transplanted between 2000 and 2007; although the rates of toxic mortality (34% at 2 years) and disease relapse (33% at 2 years) were still high [16].

While not significant, MVA showed a possible better OS for 10/10 HLA-matched UD and Haplo patients in comparison to MSD patients. The mUD showed worse OS than MSD patients. On further analysis we can draw some observations. First: the most relevant cause of HCT failure in our entire cohort was toxic death, with an estimated 2-year NRM of 29.5% globally. Despite the introduction of better supportive care, and less toxic conditioning regimens, the impact of HCT on older recipients is still substantial in terms of toxicity [17, 18]. NRM incidences varied widely across the different donor types, with recipients of 9/10 HLA mUD having

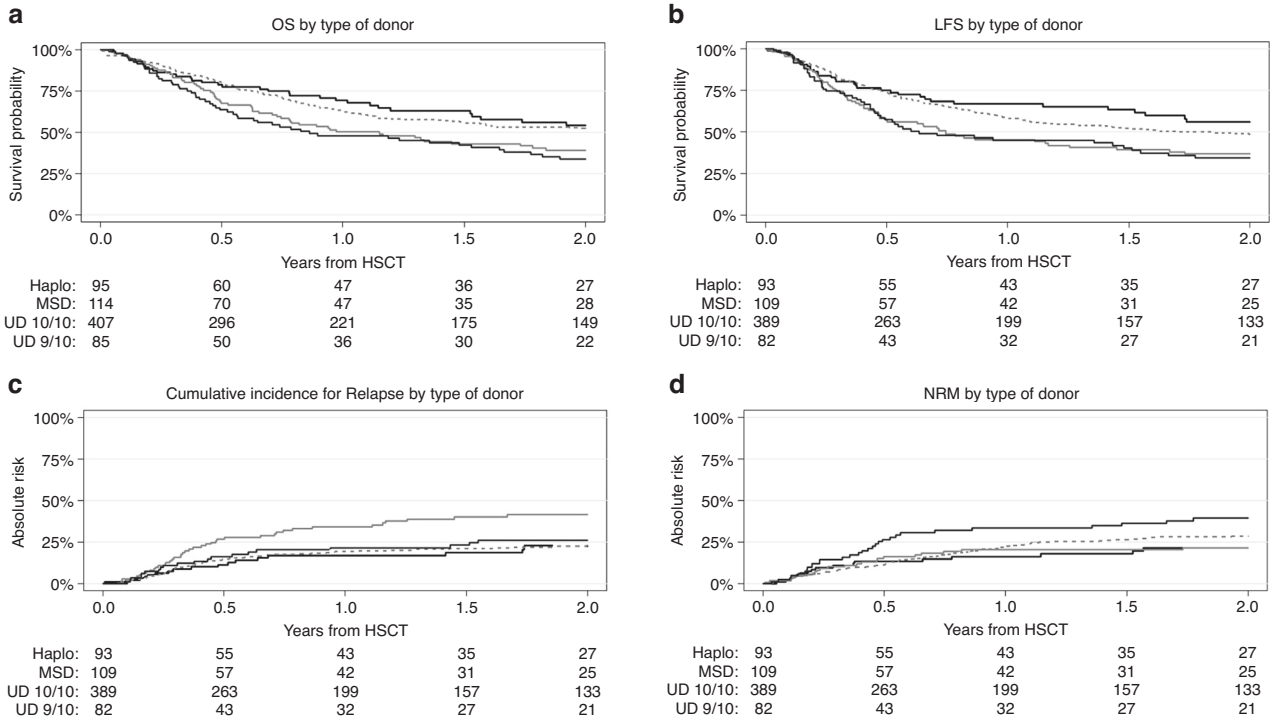

Fig. 1 Transplant Outcomes according to donor. OS (**a**) LFS (**b**) relapse incidence (**c**) and NRM (**d**) for patients transplanted from MSD, HLA 10/10 UD (dotted line), HLA 9/10 UD and haploidentical donors.

a significantly higher rate of toxicity than MSD recipients as shown by MVA, reflecting the dismal effect of HLA disparity between donor and recipient on toxic mortality [19], thus explaining the low survival rate of those patients in our analysis, and superimposable rates between recipients of MSD and Haplo transplants. The higher NRM observed among 9/10 HLA-mUD could, at least partially, be in relation to the use of in vivo T-cell depletion other than PT-CY. Not surprisingly, the use of MAC was associated with higher NRM incidence, as well as female donor for male recipient, and CMV seropositivity [20–22].

Secondly: since the intensity of the conditioning cannot be too high due to the risk of toxicity among older patients, disease relapse does represent a problem. In our analysis, cumulative RI at 2 years was 25.2% overall, but varied depending on the type of donor, with recipients of Haplo and 10/10 HLA-mUD grafts having significantly lower rate of RI than recipients of grafts from MSD. Interestingly, a recent study by the CIBMTR showed a higher RI (HR, 1.62; 95% CI: 1.32–1.97; $p < 0.001$) among adult myelodysplastic syndrome recipients using older MSD, compared to patients grafted from young MUD [23]. Other reports showed similar trends in adults with high-risk AML [24–27]. It remains difficult to explain why MSD recipients have suffered such a high incidence of disease relapse. This group of patients did not comprise an excess of high-risk disease, such as secondary AML or those with unfavorable cytogenetics; the median age of the group was superimposable on other groups, as was KPS. The percentage of MSD (13.2%) who had MAC regimen was not significantly different from those within other donor groups. Overall, 46.7% of MSD patients received in vivo T-cell depletion (55.8% for the entire study population). The only relevant difference across the four different donor types was the median (and range) year of transplantation, which was earlier for MSD. One may speculate that HCT from MSD exerts less GvL respect to Haplo or MUD, giving the less genetic disparity, both for minor histocompatibility genes, which may function as leukemia-associated specific antigens, and for HLA-DPB1 [28–31].

The intensity of transplant conditioning is relevant in overcoming disease burden and the issue is particularly delicate for elderly patients. Of note, in our analysis, there was a substantial relevant number ($n = 102$) of patients receiving MAC, which could partially explain our NRM rates. Previous reports have shown that a more intense ablative conditioning did not provide a survival benefit among older hematological patients [32]. In our analysis the use of MAC did not impact RI. Nevertheless, it remains an unsolved issue whether some patients could benefit from MAC instead of RIC. A remarkable proportion of patients ($n = 211$) received TBI-based conditioning regimens. The radiation doses delivered were not uniform, although the vast majority received low-dose 2 Gy TBI. In univariate model only, the use of low-dose radiation-based regimens was not associated with better disease control, with a trend towards higher NRM, although, in several published studies, low-dose TBI was found to be very well tolerated by older and/or infirm patients [33].

The cumulative incidence of grades III/IV acute GVHD was 7.6% overall at day-100, in line with previous reports, with favorable figures for recipients of T-cell replete Haplo HCT with PT-CY as GVHD prophylaxis and a higher incidence for 9/10 HLA-mUD, as has been shown previously [34]. Cumulative incidence of extensive chronic GVHD was superimposable between MSD and UD recipients (19-22.7%), while it was inferior for Haplo HCT, with 8.2%, in line with previous observations [35, 36]. As expected, recipients of bone marrow hematopoietic cells experienced less chronic GVHD compared with recipients of PBSC. Consequentially, patients transplanted from Haplo donors exhibited higher GRFS rates than MSD and UD recipients. Of note, a fifth of HCTs from Haplo donors were performed using bone marrow as the cell source, compared with MSD, mUD, and UD recipients who received almost exclusively PBSC. Beyond the known biases, recent studies have indicated that the addition of PT-CY to standard calcineurin inhibitor-based GVHD prophylaxis led to lower chronic GVHD incidence and higher GRFS among adult recipients of RIC regimens [37, 38].

Table 3. Results of Multivariate analysis for clinical outcomes after transplantation.

Variable		LFS		OS		RI		NRM		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
Donor Type	MSD	1		1		1		1		1		1	
	UD	0.78 (0.56–1.09)	0.15	0.79 (0.56–1.11)	0.17	0.44 (0.28–0.69)	0.001	1.48 (0.88–2.49)	0.14	0.89 (0.49–1.62)	0.7	0.75 (0.52–1.09)	0.13
	mUD	1.24 (0.82–1.88)	0.3	1.35 (0.88–2.06)	0.17	0.71 (0.39–1.27)	0.25	2.33 (1.26–4.31)	0.007	1.29 (0.63–2.66)	0.49	1.31 (0.82–2.08)	0.26
	Haploidentical	0.62 (0.39–0.99)	0.04	0.67 (0.42–1.09)	0.1	0.46 (0.25–0.87)	0.02	0.91 (0.44–1.87)	0.8	1.76 (0.87–3.55)	0.11	1.04 (0.62–1.73)	0.89
Time from diagnosis to HCT (in months)		0.99 (0.96–1.02)	0.67	0.99 (0.96–1.02)	0.64	1.01 (0.97–1.05)	0.69	0.98 (0.94–1.02)	0.35	0.98 (0.93–1.04)	0.54	0.99 (0.96–1.03)	0.73
Age at HCT (by 5 years)		1.01 (0.73–1.4)	0.96	1.08 (0.78–1.52)	0.63	0.84 (0.51–1.4)	0.51	1.17 (0.76–1.8)	0.48	0.79 (0.45–1.39)	0.42	0.89 (0.6–1.31)	0.55
Year of HCT (by 5 years)		0.92 (0.76–1.13)	0.43	0.95 (0.78–1.17)	0.66	1.06 (0.79–1.41)	0.69	0.79 (0.59–1.04)	0.09	1.15 (0.79–1.68)	0.47	1.07 (0.85–1.34)	0.58
Female donor to male recipient	No	1		1		1		1		1		1	
	Yes	1.47 (1.1–1.98)	0.01	1.64 (1.21–2.22)	0.001	1.04 (0.65–1.64)	0.88	1.94 (1.32–2.86)	0.001	0.98 (0.59–1.62)	0.94	1.33 (0.95–1.85)	0.1
CMV patient	Negative	1		1		1		1		1		1	
	Positive	1.08 (0.82–1.43)	0.56	1.19 (0.89–1.6)	0.24	0.79 (0.53–1.17)	0.23	1.5 (1.01–2.22)	0.04	0.91 (0.58–1.44)	0.7	0.88 (0.64–1.22)	0.44
CMV donor	Negative	1		1		1		1		1		1	
	Positive	1.1 (0.85–1.41)	0.47	1.12 (0.86–1.46)	0.39	1.15 (0.78–1.68)	0.48	1.04 (0.74–1.47)	0.82	1.15 (0.76–1.74)	0.51	1.31 (0.97–1.77)	0.08
Myeloablative regimen	No	1		1		1		1		1		1	
	Yes	1.23 (0.89–1.71)	0.2	1.37 (0.98–1.92)	0.07	0.88 (0.51–1.51)	0.64	1.54 (1.01–2.35)	0.04	1.2 (0.68–2.13)	0.52	1.59 (1.1–2.28)	0.01
Cytogenetics	favorable/int	1		1		1		1		1		1	
	adverse	1.37 (0.99–1.9)	0.055	1.47 (1.05–2.04)	0.02	1.48 (0.92–2.39)	0.1	1.29 (0.82–2.02)	0.27	1.36 (0.86–2.14)	0.18	1.21 (0.84–1.75)	0.31
	NA/failed	1.2 (0.9–1.6)	0.21	1.33 (0.99–1.79)	0.06	1.37 (0.91–2.08)	0.13	1.06 (0.7–1.58)	0.79	0.53 (0.3–0.94)	0.03	1.4 (1–1.95)	0.048
sAML	No	1		1		1		1		1		1	
	Yes	1.03 (0.8–1.32)	0.82	1.01 (0.78–1.31)	0.93	0.96 (0.66–1.4)	0.83	1.07 (0.76–1.5)	0.71	1.35 (0.9–2.03)	0.14	1.13 (0.84–1.52)	0.41
Karnofsky	<90	1		1		1		1		1		1	
	>=90	0.76 (0.59–0.97)	0.03	0.75 (0.58–0.97)	0.03	0.74 (0.51–1.06)	0.1	0.76 (0.54–1.07)	0.11	0.85 (0.57–1.27)	0.42	0.84 (0.63–1.12)	0.24

CI confidence interval, *MSD* matched sibling donor, *UD* unrelated donor, *mUD* mismatched unrelated donor, *GVHD* graft-versus-host disease, *NRM* non-relapse mortality, *LFS* leukemia-free survival, *OS*, overall survival, *RI* relapse incidence, GRFS graft-versus-host disease/relapse-free survival, *sAML* secondary acute myeloid leukemia, *HCT* allogeneic hematopoietic cell transplantation, *CMV* cytomegalovirus.

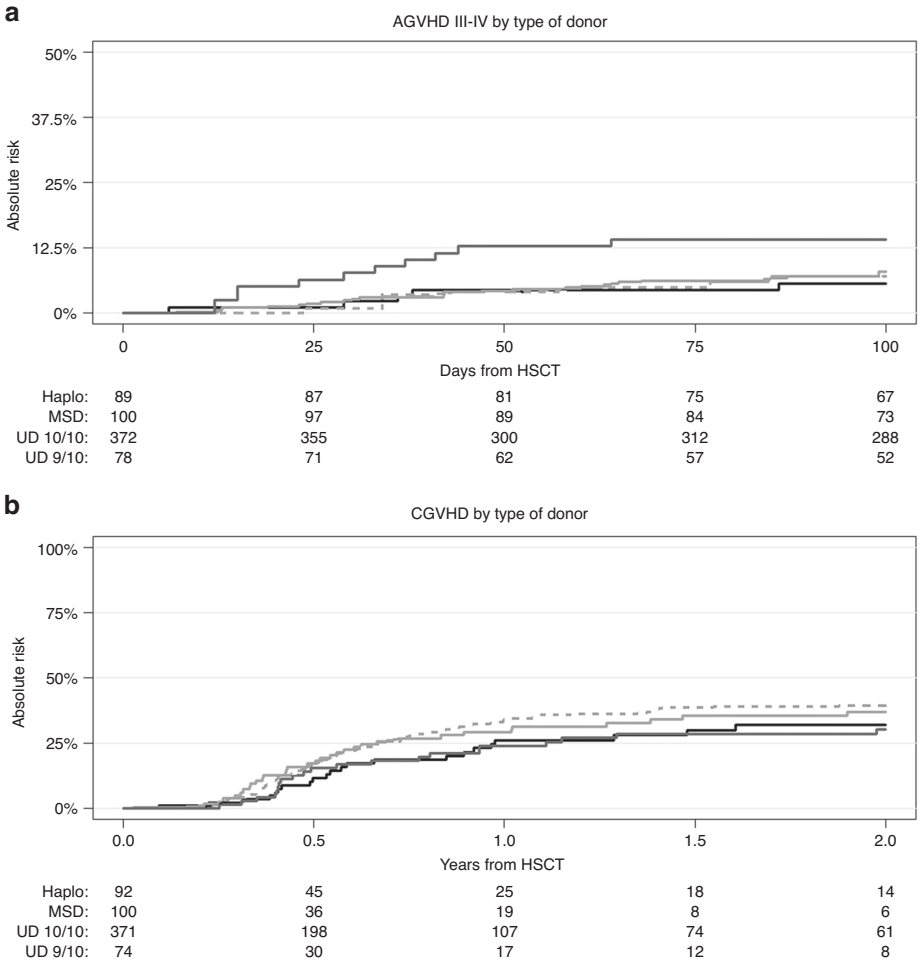

Fig. 2 Graft-versus-Host disease. Cumulative incidence of grades III/IV acute GVHD (**a**) and chronic GVHD (**b**) for patients transplanted from MSD, HLA 10/10 UD (dotted line), HLA 9/10 UD and haploidentical donors.

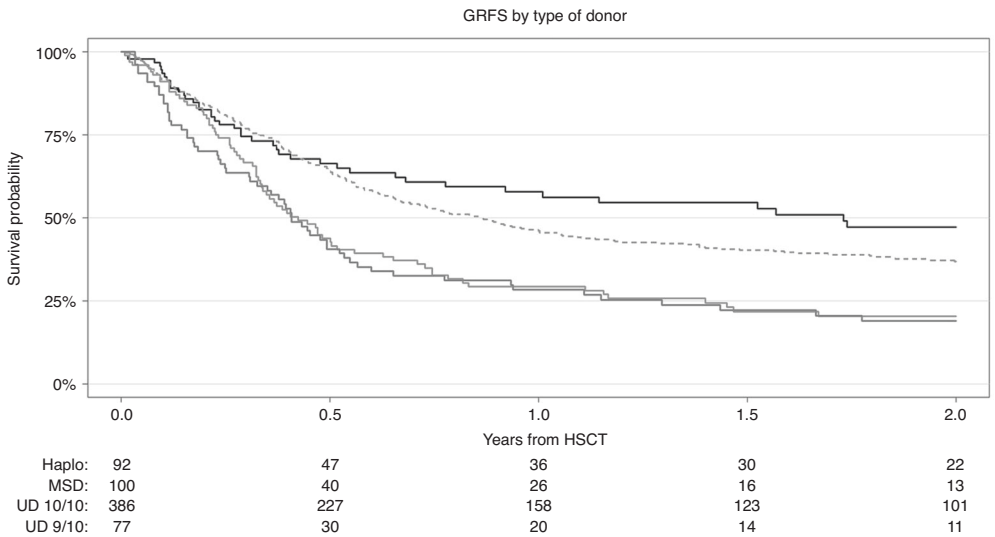

Fig. 3 Grade ≥ 2 acute GvHD/relapse-free survival after trasplantation. GRFS for patients transplanted from MSD, HLA 10/10 UD (dotted line), HLA 9/10 UD and haploidentical donors.

Our study has its own limitations: first of all, we should interpret the results taking into account the fact that our study cohort is made up of a highly selected physically fit (HCT-CI less than 3 for more than 70%) patient population, receiving an allogeneic HCT in their 8th decade of life, introducing a not negligible selection bias. Second, the study retrospective nature led to a comparison of clinical outcomes between patients receiving different HCT platforms with different conditioning regimens and GVHD

prophylaxis. Additional immunosuppressive agents, such as Campath, or T-cell depletion strategies, such as PT-CY, added some obvious difficulties in data interpretation. Missing information on AML biology such as molecular and cytogenetics does not allow to properly identify separate clinical-biological AML entities, and they do represent an obvious limitation of the study. Given the importance of measurable residual disease (MRD) as a single robust factor influencing clinical outcomes after HCT, lack of data on MRD at the time of HCT is extremely relevant [39–41]. Implementing data retrieval in this context is essential to expand our knowledge and refine indications for transplant. Baseline clinical and molecular data could hopefully offer vital information, guiding transplant physicians to specific personalized therapeutic interventions aimed at reducing RI or the risk of toxic death [42]. The obvious limitation of the study lies in the inclusion of PT-CY for GvHD prophylaxis exclusively in haploidentical donors cohort; accumulating evidences suggest that adding PTCY is feasible and effective also in the context of HLA-mismatched unrelated donors [43, 44].

In conclusion, selected older AML patients could benefit from an allogeneic HCT in CR1, with prolonged survival and acceptable rates of GRFS. It is advisable that patients in their eighth decade with AML in CR1, with good physical fitness, without relevant comorbidities, could be referred for allogeneic HCT, given historical data showing an advantage for HCT with respect to chemotherapy-based strategies. Novel non-intensive therapeutic strategies hold promise for improving response rates before HCT. The favorable clinical outcomes seen among recipients of T-cell replete Haplo transplants must be validated with prospective clinical trials and further explored with the use of PTCY for GvHD prophylaxis also with non-haploidentical donors.

DATA AVAILABILITY

Published data are available on specific request via email to the corresponding author.

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AUTHOR CONTRIBUTIONS

EM analyzed the data and wrote the manuscript; MN contributed to the statistical analysis. AN and MM critically appraised the paper. All the Authors approved the final version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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