Outcomes of hematopoietic stem cell transplantation from unmanipulated haploidentical versus matched sibling donor in patients with acute myeloid leukemia in first complete remission with intermediate or high-risk cytogenetics: a study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation

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ABSTRACT

Allogeneic hematopoietic stem cell transplantation is the optimal care for patients with high-risk or intermediate - acute myeloid leukemia. In patients lacking matched sibling donor, haploidentical donors are an option. We compared outcomes of unmanipulated (Haplo) to matched sibling donor transplant in acute myeloid leukemia patients in first complete remission. Included were intermediate and high-risk acute myeloid leukemia in first complete remission undergoing Haplo and matched sibling donor transplant from 2007-2015, and reported to the ALWP of the EBMT. A propensity score technique was used to confirm results of main analysis: 2 matched sibling donors were matched with 1 Haplo. We identified 2654 pts (Haplo =185; matched sibling donor =2469), 2010 with intermediate acute myeloid leukemia (Haplo=122; matched sibling donor =1888) and 644 with high-risk acute myeloid leukemia (Haplo =63; matched sibling donor =581). Median follow up was 30 (range 1-116) months. In multivariate analysis, in intermediate - acute myeloid leukemia patients, Haplo resulted in lower leukemia-free survival (Hazard Ratio 1.74; $P<0.01$), overall-survival (HR 1.80; $P<0.01$) and GvHD-free-relapse-free survival (Hazard Ratio 1.32; $P<0.05$) and higher graft-*versus*-host disease (GvHD) non-relapse mortality (Hazard Ratio 3.03; $P<0.01$) as compared to matched sibling donor. In high-risk acute myeloid leukemia, no differences were found in leukemia-free survival, overall-survival, and GvHD-free- relapse-free survival according to donor type. Higher

grade II-IV acute GvHD was observed for Haplo in both high-risk (Hazard Ratio 2.20; *P*<0.01) and intermediate risk (Hazard Ratio 1.84; *P*<0.01). A trend for a lower Relapse-Incidence was observed in Haplo among high-risk acute myeloid leukemia (Hazard Ratio 0.56; *P*=0.06). The propensity score analysis confirmed results. Our results underline that matched sibling donor is the first choice for acute myeloid leukemia patients in first complete remission. On the other hand, results of Haplo transplants are similar to matched sibling donor transplants in acute myeloid leukemia patients with high risk cytogenetics.

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative treatment for patients with acute myeloid leukemia (AML).[1] However, a human leukocyte antigen (HLA)-identical sibling[2,3] is available in only 25-35% of the patients.[4] For patients lacking a full matched sibling donor (MSD), other stem cell sources are available such as unrelated donors,[5] umbilical cord blood units,[6] or HLA-mismatched family donors (Haplo).[7,8] The advantage of the latter is the rapid availability of the donors both for the transplant procedure and for subsequent adoptive immunotherapies. Initial concerns with the Haplo-HSCT were the high rate of graft failure, of severe graft-*versus*-host disease (GvHD) due to the multiple class I and II HLA disparities between donor and recipient, and the high non-relapse mortality (NRM).[9,10,11] Advances in HLA typing, optimization of GvHD prophylaxis and other transplantation techniques allowed outcome improvements,[8] such as the use of non T-cell depleted (TCD) unmanipulated grafts with new strategies to modulate donor T-cell alloreactivity. In particular, the use of post-transplant high-dose cyclophosphamide (PTCY) or the addition of anti thymocyte globulin (ATG) to standard GvHD prophylaxis ensured higher rates of engraftment while keeping an acceptable incidence of GvHD.[12,13,14]

This contributed to the increase in the number of unmanipulated Haplo-HSCT performed in recent years.[15]

Single center or registry-based studies have reported similar outcomes between Haplo-HSCT and unrelated or cord blood allo-HSCT for patients with hematological malignancies.[14,16,17,18]

Data comparing Haplo -HSCT to MSD-HSCT in AML patients are limited. In a recent prospective multicenter non-randomized study from China, Wang *et al*.[19] showed in a very young cohort of AML patients (median age of 28 years in the Haplo group) similar outcomes for Haplo and MSD-HSCT in AML patients in first complete remission (CR1). Similarly, Yoon *et al*.[20] analyzed long-term outcomes of 561 patients with intermediate (n=417) or poor risk (n=144) AML that underwent HSCT in CR1 from various donors including from MSD and Haplo. In poor risk AML, the authors observed a 5-year disease-free survival (DFS) of 47% *versus* 60% (*P*<0.01) for MSD and Haplo, respectively; while in intermediate risk AML, DFS was 66% and 68% (*P*=0.08) for MSD and Haplo, respectively.

Herein, we conducted a registry-based study of adult patients undergoing either an unmanipulated Haplo or a MSD allo-HSCT for high or intermediate risk AML in CR1, reported to the Acute Leukemia Working Party (ALWP) of EBMT.

Methods

We retrospectively analyzed adult patients (≥18 years) diagnosed with AML with intermediate or unfavorable cytogenetics who underwent their first allo-HSCT in CR1 between 2007 and 2015, from either a MSD or Haplo donor, and whose data were reported to the ALWP of the EBMT.

The EBMT is a voluntary working group of more than 500 transplant centers that are required to report all consecutive stem cell transplantations and follow up once a year. Audits are routinely performed to determine the accuracy of the data. This 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.

Patients were stratified according to cytogenetic status at diagnosis in intermediate or high risk, according to the previous definition from Grimwade *et al*.[21] Of note, included in the Haplo group, were only patients receiving an unmanipulated graft with the use of *in vivo* TCD or PTCY. *Ex vivo* graft manipulation was an exclusion criteria.

Conditioning regimen was defined myeloablative (MAC) when containing total body irradiation (TBI) with a dose >6 Gray or a total dose of busulfan (Bu) >8 mg/kg or >6.4 mg/kg when administered orally or intravenously, respectively. All other regimens were defined as RIC.[22]

Primary end-point was leukemia-free survival (LFS), defined as the probability of being alive and disease-free at any time point. Both death and relapse were considered events. Patients alive and in CR were censored at their last follow up. Overall survival (OS) was defined as the probability of being alive at any time point. Other secondary endpoints were engraftment, acute (aGvHD) and chronic (cGvHD) GvHD, relapse incidence (RI), non-relapse mortality (NRM) and refined graft-*versus*-host/relapse free survival (GRFS),[23] defined as being alive with neither grade III-IV aGvHD, severe cGvHD nor disease relapse at any time point. Modified Glucksberg criteria and revised Seattle criteria were used to grade aGvHD[24] and cGvHD,[25] respectively. Engraftment was defined as achieving an absolute neutrophil count greater than or equal to 0.5×10^9/L for three consecutive days. NRM was defined as death from any cause without previous relapse or progression. Median values and ranges were used for continuous variables and percentages for categorical variables. Patient-, disease- and transplant-related variables were compared using χ^2 or Fischer exact test for categorical variables, and Mann–Whitney test for continuous variables. Probabilities of OS, LFS and GRFS were calculated using Kaplan-Meier method.[26] Cumulative incidence functions (CIF) were used to estimate RI and NRM in a competing risks setting. To study GvHD, death and relapse were considered as competing events. Univariate analyses were performed using the log rank test for OS, LFS and GRFS, while the Gray test was used for CIF. Multivariate analyses adjusted for differences between the groups were performed using Cox proportional hazards regression model.[27]

All interactions between donor type and other covariates were tested; a significant interaction according to cytogenetics has been found, thus a stratification (intermediate or high cytogenetics risk AML) with two separate analysis was made.

Propensity score matching was also performed to reduce or eliminate confounding effects. Two MSD were matched with each Haplo using the nearest neighbor or exact matching.[28] Matching was done without replacement. Included in the propensity score model were: age, year of allo-HSCT, time from diagnosis to allo-HSCT, conditioning regimen (RIC), source of stem cells, cytogenetics, patient and donor CMV serology status.

All tests were two-sided and P values < 0.05 were considered statistically significant. Analyses were performed using the R statistical software version 3.2.3 (available online at http://www.R-project.org), and propensity score analysis was performed using the 'MatchIt'.[29]

Results

Patients, disease and transplant characteristics

Patients and transplant characteristics are summarized in Table 1. Median follow up was 22 (range 3-96) months and 31 (range 1-116) months for Haplo and MSD, respectively (P<0.01). We identified a total of 2654 patients (Haplo=185; MSD=2469), including 2010 intermediate AML (Haplo=1122; MSD=1888) and 644 high risk-AML (Haplo=163; MSD=581) transplanted in 227 EBMT centers. Median age at allo-HSCT was 50 (range 18-74) years for both Haplo and MSD (P=0.63). There were some differences between the two groups: Haplo underwent allo-HSCT more recently compared to MSD recipients (2014 *versus* 2010; P<0.01) and had a longer time from diagnosis to allo-HSCT (6 *versus* 5 months, P<0.01); furthermore, in

Table 1. Patient, disease and transplant characteristics.

Characteristic (%)	Haplo (n=185)	MSD (n=2469)	*P*
Median age, years (range)	50 (18-74)	50 (18-75)	0.63
Median year of allo-HSCT (range)	2014 (2007-2015)	2010 (2007-2015)	<0.01
Interval from diagnosis to allo-HSCT, months (range)	6 (1-17)	5 (1-18)	<0.01
Cytogenetics			
Intermediate	122 (66)	1888 (76)	<0.01
High risk	63 (34)	581 (24)	
Patient's sex			
Male	103 (56)	1296 (53)	0.41
Female	82 (44)	1172 (47)	
Donor's sex			
Male	96 (52)	1322 (54)	0.43
Female	89 (48)	1140 (46)	
Patient CMV serostatus			
Negative	28 (15)	777 (32)	<0.01
Positive	155 (85)	1660 (68)	
Donor CMV serostatus			
negative	51 (28%)	927 (38%)	<0.01
positive	132 (72%)	1492 (62%)	
Missing	2	50	
Conditioning regimen			
MAC	93 (50)	1302 (53)	0.52
RIC	92 (50)	1167 (47)	
Stem cell source			
BM	92 (50)	473 (19)	<0.01
PBSC	93 (50)	1996 (81)	
GVHD prophylaxis			<0.01
CsA alone	4 (2)	470 (19)	
CsA + MMF	4 (2)	487 (20)	
Csa + MTX	7 (4)	1273 (51)	
PT-CY	137 (74)	36 (2)	
Other	33 (18)	182 (7)	
Missing	0	21 (1)	
In vivo TCD	54 (31)	863 (35)	0.30
Median follow-up, months (range)	22 (3-96)	31 (1-116)	<0.01

Haplo: haploidentical family donor; MSD: matched sibling donor; allo-HSCT: allogeneic hematopoietic stem cell transplantation; CMV: cytomegalovirus; MAC: myeloablative conditioning regimen; RIC: reduced intensity conditioning regimen; BM: bone marrow; PBSC: peripheral blood stem cells; CSA: cyclosporine; MMF: mycophenolate mofetil; MTX: methotrexate; PT-CY: post-transplant cyclophosphamide; TCD: *in vivo* T-cell depletion.

the Haplo group there was a higher proportion of high-risk AML (34% *versus* 24% in MSD, P<0.01), bone marrow (BM) as stem cell source (50% *versus* 19% in MSD; *P*<0.01) and CMV positive donors (72% *versus* 62% in MSD; *P*<0.01). Conditioning regimen was MAC in approximately 50% of cases in both Haplo and MSD (*P*=0.52). In the Haplo group, the most frequently used MAC contained Thiotepa-Busulfan-Fludarabine, while the most frequent RIC contained cyclophosphamide and 2 or 4 Gy TBI. In the MSD group, the most frequently used MAC and RIC regimen were Busulfan-Cyclophosphamide and Busulfan-Fludarabine, respectively. Details on conditioning regimens are reported in the Online Supplementary Table. Among Haplo recipients, 137 (74%) received PTCY and 54 (31%) received ATG as GvHD prophylaxis.

Univariate analysis for the whole population

The results of univariate analysis are summarized in Table 2A. A higher engraftment rate was observed in MSD recipients (99% *versus* 96%, *P*<0.01), with a shorter median time to engraftment in this group (16 *versus* 18 days in Haplo, *P*<0.01)

Higher incidence of grade II-IV aGvHD was found in Haplo (21% *versus* 31%, *P*<0.01) while cGvHD was lower as compared to MSD (33% *versus* 35%, *P*=0.05). Main causes of death were disease recurrence (in 30% *versus* 59%), GvHD in 16% *versus* 18% and infections in 33% *versus* 12% of Haplo and MSD, respectively.

At 2 years, CI of relapse was 19% *versus* 24% (*P*=0.10) and NRM was 23% *versus* 10% (*P*<0.01) in Haplo and MSD recipients, respectively. The probability of LFS and OS were 58% *versus* 67% (*P*<0.01) and 68% *versus* 76% (*P*<0.01), in Haplo and MSD, respectively. Probability of GRFS was 47% *versus* 50% (*P*=0.25), respectively.

Multivariate analysis for the whole population

In a multivariate analysis adjusted on the main differences between the two groups (Table 3A), Haplo was associated with a higher risk of grade II-IV aGvHD (HR=1.94; 95% CI: 1.38-2.73; *P*<0.01), a higher NRM (HR=2.56; 95% CI:1.73-3.77; *P*<0.01), a lower LFS (HR=1.33; 95% CI: 1.03-1.71; *P*<0.04) and a lower OS (HR=1.34; 95% CI: 1.03-1.75; *P*<0.04).

Moreover, due to a significant interaction between donor type and cytogenetic risk on LFS (*P*<0.01), all further analyses were stratified on cytogenetic group.

Outcomes according to cytogenetics: intermediate and high-risk AML

Intermediate risk AML

The results of univariate analysis in this group are summarized in Table 2B. Grade II-IV aGvHD was 29% *versus* 20% (*P*<0.03) for Haplo and MSD recipients, respectively. At 2 years, CI of cGvHD was 30% *versus* 36% (*P*<0.02) for Haplo and MSD recipients, respectively. The probability of LFS and OS were 56 % *versus* 70% (*P*<0.01) and 68% *versus* 79% (P<0.01) in Haplo and MSD, respectively. Probability of GRFS was 45% *versus* 54% (*P*<0.05), in Haplo and MSD, respectively. CI of relapse was 18% *versus* 20% (*P*=0.52) and NRM was 26% *versus* 10% (*P*<0.01) in Haplo and MSD recipients, respectively.

In multivariate analysis, Haplo was associated with a higher risk of grade II-IV aGvHD (HR 1.84; 95% CI 1.20-2.82; *P*<0.01), higher NRM (HR 3.03; 95% CI 1.98-4.62; *P*<0.01), lower LFS (HR 1.74; 95% CI 1.30-2.32; *P*<0.01), OS (HR 1.80; 95% CI 1.32-2.45; *P*<0.01) and GRFS (HR 1.32 ; 95% CI 1.01-1.72; *P*<0.05). No significant differences were found for cGvHD and RI. Results of multivariate analysis for donor type and other factors associated with the main outcomes are reported in table 3B.

High risk AML

The results of univariate analysis are summarized in table 2C For Haplo and MSD recipients, grade II-IV aGvHD was 36% *versus* 24% (*P*<0.04) and cGvHD was

Table 2. Results of univariate analysis for main outcomes at 2 years after allo-HSCT according to donor type (A) in patients with intermediate (B) and high risk (C) AML.

A) Outcome	RI % ±s.d.	NRM % ±s.d.	LFS % ±s.d.	OS % ±s.d.	Gr. II-IV aGvHD % ±s.d.	cGvHD% ±s.d.	GRFS% ±s.d.
Haplo	19±6	23±6	58±6	68±6	31±7	33±6	47±8
MSD	24±2	10±2	67±4	76±2	21±2	35±2	50±2
P	0.10	<0.01	<0.01	<0.01	<0.01	0.05	0.25
B) Outcome	**RI % ±s.d.**	**NRM % ±s.d.**	**LFS % ±s.d.**	**OS % ±s.d.**	**Gr. II-IV aGvHD % ±s.d.**	**cGvHD% ±s.d.**	**GRFS% ±s.d.**
Haplo	18±7	26±8	56±9	68±8	29±8	30±9	45±9
MSD	20±3	10±2	70±2	79±2	20±2	36±2	54±2
P	0.52	<0.01	<0.01	<0.01	<0.03	<0.02	<0.05
C) 2-years outcome	**RI% ±s.d**	**NRM% ±s.d**	**LFS% ±s.d**	**OS % ±s.d**	**aGvHD gr II-IV % ±s.d**	**cGvHD % ±s.d**	**GRFS % ±s.d**
Haplo	21±9	18±9	61±13	67±12	36±12	39±12	49±13
MSD	36±4	10±3	55±4	66±4	24±3	33±4	40±4
P	<0.02	0.16	0.14	0.26	<0.04	0.79	0.17

RI: relapse incidence; s.d.: standard deviation; NRM: non-relapse mortality; LFS: leukemia-free survival; OS: overall survival; GRFS: refined graft-*versus*-host disease/relapse free survival; aGvHD: acute graft-*versus*-host disease; cGvHD: chronic-graft-*versus* host disease; Haplo: haploidentical donor; MSD: matched sibling donor.

39% *versus* 33% (*P*=0.79). The probability of LFS and OS were 61 % *versus* 55% (*P*=0.14) and 67% *versus* 66% (*P*=0.26) in Haplo and MSD, respectively. Probability of GRFS was 49% *versus* 40% (*P*=0.17), in Haplo and MSD, respectively. CI of relapse was 21% *versus* 36% (*P*<0.02) and NRM was 18% *versus* 10% (*P*=0.16) for Haplo and MSD, respectively.

In multivariate analysis, Haplo was associated with a higher risk of grade II-IV aGvHD (HR 2.20; 95% CI 1.29-3.74; *P*<0.01) and a trend for a lower RI (HR 0.56; 95% CI 0.31-1.01; P=0.06). No significant differences were found for other outcomes. Results of multivariate analysis for donor type and other factors associated with the main outcomes are reported in table 3C.

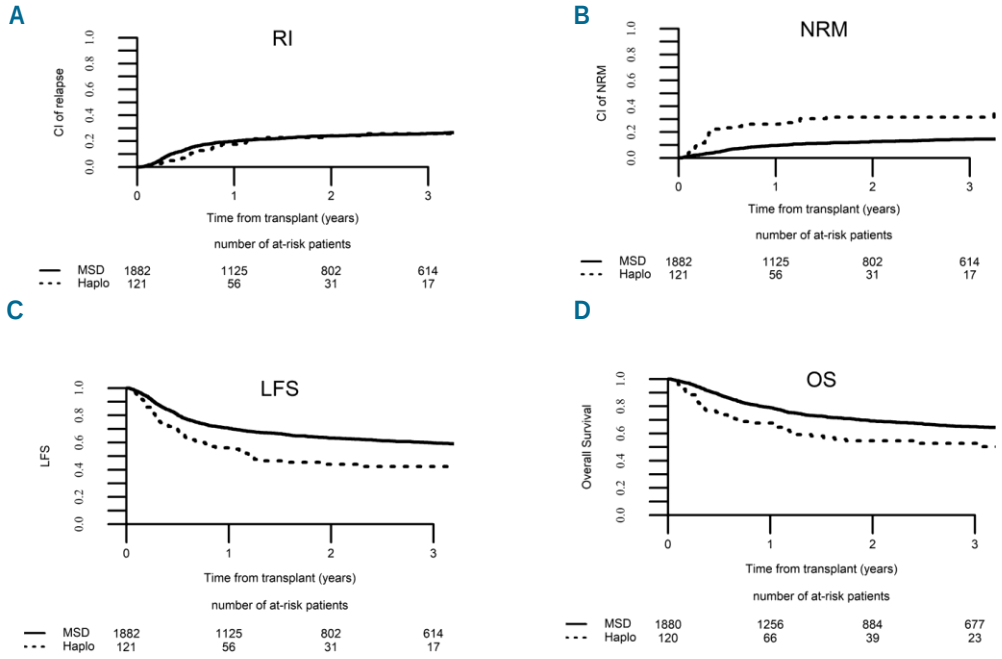

Figure 1. Outcomes at two years according to pair-matched analysis in patients with intermediate-risk acute myeloid leukemia. (A) Relapse-incidence. (B) Non-relapse mortality. (C Leukemia-free survival. (D) Overall survival.

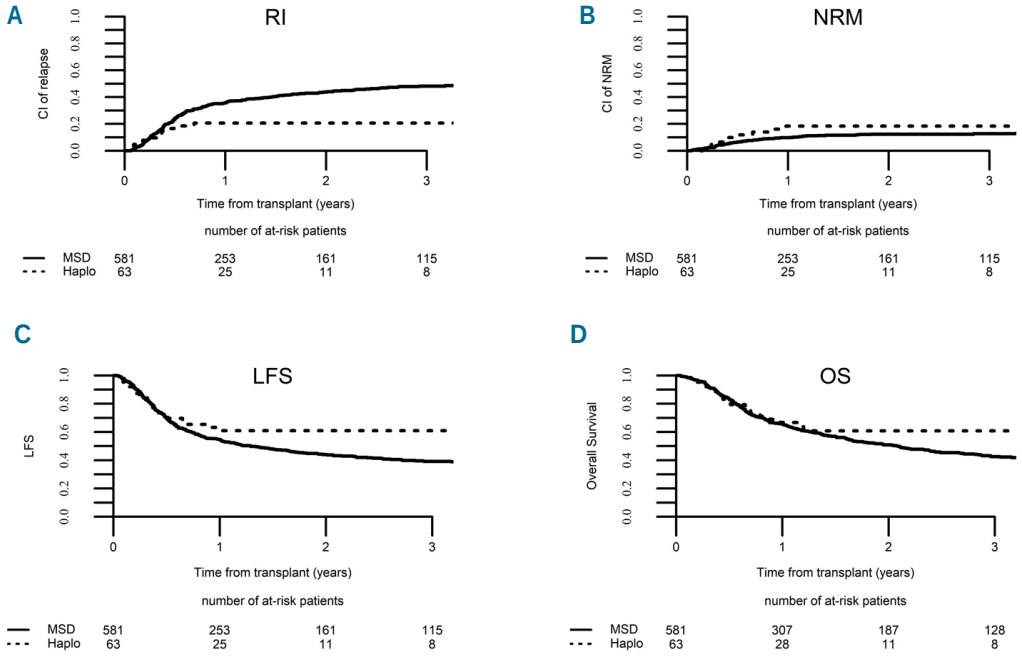

Figure 2. Outcomes at two years according to pair-matched analysis in patients with high-risk acute myeloid leukemia. (A) Relapse-incidence. (B) Non-relapse mor- tality. (C) Leukemia-free survival. (D) Overall survival.

Table 3. Results of multivariate analysis of main outcomes after HSCT in the entire population (A) and in patients with intermediate (B) or high risk (c) AML.

A) Variable	HR (95% CI)	P
RI		
Haplo *versus.* MSD	0.86 (0.60-1.22)	0.41
Age (incremental age of 10 years)	1.03 (0.97-1.11)	0.27
Year of allo-HSCT	1.00 (0.97-1.04)	0.62
RIC *versus* MAC	1.12 (0.93-1.34)	0.21
PBSC *versus* BM	0.95 (0.78-1.17)	0.66
Female to male recipient *versus* other	0.91 (0.76-1.09)	0.33
Patient CMV seropositivity	1.07 (0.90-1.27)	0.43
Donor CMV seropositivity	0.90 (0.76-1.05)	0.20
Poor cytogenetics *versus* other	1.90 (1.62-2.22)	<0.01
Time from diagnosis to allo-HSCT > median	0.94 (0.90-0.98)	<0.01
NRM		
Haplo *versus* MSD	2.56 (1.73-3.77)	<0.01
Age (incremental age of 10 years)	1.24 (1.11-1.37)	<0.01
Year of allo-HSCT	0.96 (0.92-1.01)	0.17
RIC *versus* MAC	0.79 (0.61-1.03)	0.08
PBSC *versus* BM	0.98 (0.73-1.31)	0.89
Female to male recipient *versus* other	1.33 (1.05-1.67)	0.01
Patient CMV seropositivity	1.22 (0.93-1.59)	0.13
Donor CMV seropositivity	1.28 (1.00-1.64)	0.04
Poor cytogenetics *versus* other	1.03 (0.79-1.34)	0.79
Time from diagnosis to allo-HSCT > median	1.00 (0.96-1.05)	0.76
LFS		
Haplo *versus* MSD	1.33 (1.03-1.71)	<0.04
Age (incremental age of 10 years)	1.09 (1.03-1.16)	<0.01
Year of allo-HSCT	0.99 (0.97-1.02)	0.76
RIC *versus* MAC	1.00 (0.86-1.16)	0.93
PBSC *versus* BM	0.96 (0.81-1.13)	0.65
Female to male recipient *versus* other	1.04 (0.91-1.20)	0.50
Patient CMV seropositivity	1.11 (0.96-1.29)	0.13
Donor CMV seropositivity	1.00 (0.87-1.15)	0.94
Poor cytogenetics *versus* other	1.59 (1.39-1.81)	<0.01
Time from diagnosis to allo-HSCT > median	0.97 (0.94-1.00)	0.08
OS		
Haplo *versus* MSD	1.34 (1.03-1.75)	<0.04
Age (incremental age of 10 years)	1.15 (1.08-1.22)	<0.01
Year of allo-HSCT	0.99 (0.96-1.02)	0.71
RIC *versus* MAC	0.94 (0.81-1.09)	0.45
PBSC *versus* BM	1.04 (0.88-1.23)	0.60
Female to male recipient *versus* other	1.09 (0.94-1.27)	0.21
Patient CMV seropositivity	1.15 (0.99-1.34)	0.06
Donor CMV seropositivity	1.01 (0.87-1.16)	0.87
Poor cytogenetics *versus* other	1.71 (1.49-1.97)	<0.01
Time from diagnosis to allo-HSCT > median	0.97 (0.94-1.01)	0.17
GRFS		
Haplo *versus* MSD	1.17 (0.92-1.48)	0.18
Age (incremental age of 10 years)	1.07 (1.01-1.12)	<0.01
Year of allo-HSCT	0.98 (0.96-1.00)	0.12
RIC *versus* MAC	0.90 (0.79-1.03)	0.14
PBSC *versus* BM	1.07 (0.92-1.24)	0.36

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Female to male recipient *versus* other	1.20 (1.07-1.36)	<0.01
Patient CMV seropositivity	1.04 (0.92-1.18)	0.47
Donor CMV seropositivity	1.03 (0.92-1.16)	0.55
Poor cytogenetics *versus* other	1.40 (1.24-1.58)	<0.01
Time from diagnosis to allo-HSCT > median	0.98 (0.95-1.00)	0.17
aGvHD II-IV		
Haplo *versus* MSD	1.94 (1.38-2.73)	<0.01
Age (incremental age of 10 years)	1.00 (0.92-1.08)	0.98
Year of allo-HSCT	0.96 (0.92-0.99)	0.02
RIC *versus* MAC	0.69 (0.55-0.86)	<0.01
PBSC *versus* BM	0.98 (0.77-1.24)	0.87
Female to male recipient *versus* other	1.31 (1.08-1.59)	<0.01
Patient CMV seropositivity	0.83 (0.67-1.02)	0.09
Donor CMV seropositivity	1.17 (0.96-1.43)	0.11
Poor cytogenetics *versus* other	1.23 (1.01-1.50)	0.03
Time from diagn to allo-HSCT > median	0.95 (0.91-1.00)	0.04
cGvHD		
Haplo *versus* MSD	0.80 (0.57-1.13)	0.21
Age (incremental age of 10 years)	1.09 (1.02-1.16)	<0.01
Year of allo-HSCT	0.99 (0.96-1.02)	0.88
RIC *versus* MAC	0.77 (0.65-0.92)	<0.01
PBSC *versus* BM	1.15 (0.94-1.40)	0.16
Female to male recipient *versus* other	1.42 (1.22-1.65)	<0.01
Patient CMV seropositivity	0.92 (0.78-1.07)	0.31
Donor CMV seropositivity	1.05 (0.91-1.23)	0.46
Poor cytogenetics *versus* other	1.04 (0.88-1.22)	0.62
Time from diagnosis to allo-HSCT > median	0.99 (0.96-1.02)	0.76

B)	Variable	HR (95% CI)	*P*
RI			
Haplo *versus* MSD	1.12 (0.74-1.71)	0.58	
Age (incremental age of 10 years)	0.99 (0.91-1.08)	0.80	
Year of allo-HSCT	1.01 (0.98-1.05)	0.47	
RIC *versus* MAC	1.25 (1.01-1.57)	<0.05	
PBSC *versus* BM	0.98 (0.78-1.24)	0.86	
Female to male recipient *versus* other	0.87 (0.70-1.08)	0.20	
Patient CMV seropositivity	0.99 (0.80-1.22)	0.93	
Donor CMV seropositivity	1.06 (0.87-1.30)	0.55	
Time from diagnosis to allo-HSCT > median	0.94 (0.89-0.98)	<0.01	
NRM			
Haplo *versus* MSD	3.03 (1.98-4.62)	<0.01	
Age (incremental age of 10 years)	1.27 (1.12-1.43)	<0.01	
Year of allo-HSCT	0.99 (0.94-1.05)	0.85	
RIC *versus* MAC	0.86 (0.64-1.15)	0.30	
PBSC *versus* BM	1.11 (0.80-1.53)	0.54	
Female to male recipient *versus* other	1.29 (1.00-1.67)	0.06	
Patient CMV seropositivity	1.15 (0.86-1.55)	0.35	
Donor CMV seropositivity	1.41 (1.06-1.87)	<0.02	
Time from diagnosis to allo-HSCT > median	0.99 (0.94-1.04)	0.69	
LFS			
Haplo *versus* MSD	1.74 (1.30-2.32)	<0.01	
Age (incremental age of 10 years)	1.08 (1.01-1.16)	<0.04	
Year of allo-HSCT	1.01 (0.98-1.04)	0.59	

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RIC *versus* MAC	1.09 (0.92-1.30)	0.32
PBSC *versus* BM	1.02 (0.85-1.23)	0.82
Female to male recipient *versus* other	1.02 (0.87-1.20)	0.80
Patient CMV seropositivity	1.04 (0.88-1.24)	0.63
Donor CMV seropositivity	1.17 (0.99-1.38)	0.06
Time from diagnosis to allo-HSCT > median	0.96 (0.93-1.00)	<0.04
OS		
Haplo *versus* MSD	1.80 (1.32-2.45)	<0.01
Age (incremental age of 10 years)	1.14 (1.06-1.23)	<0.01
Year of allo-HSCT	1.01 (0.97-1.04)	0.72
RIC *versus* MAC	1.01 (0.84-1.22)	0.91
PBSC *versus* BM	1.13 (0.92-1.38)	0.25
Female to male recipient *versus* other	1.09 (0.92-1.30)	0.33
Patient CMV seropositivity	1.10 (0.92-1.32)	0.30
Donor CMV seropositivity	1.15 (0.96-1.37)	0.13
Time from diagnosis to allo-HSCT > median	0.94 (0.93-1.01)	0.13
GRFS		
Haplo *versus* MSD	1.32 (1.01-1.72)	<0.05
Age (incremental age of 10 years)	1.07 (1.01-1.13)	<0.03
Year of allo-HSCT	0.99 (0.96-1.02)	0.44
RIC *versus* MAC	0.97 (0.83-1.13)	0.68
PBSC *versus* BM	1.02 (0.87-1.20)	0.77
Female to male recipient *versus* other	1.22 (1.06-1.40)	<0.01
Patient CMV seropositivity	1.06 (0.91-1.22)	0.46
Donor CMV seropositivity	1.16 (1.01-1.33)	<0.04
Time from diagnosis to allo-HSCT > median	0.97 (0.95-1.01)	0.11
aGvHD II-IV		
Haplo *versus* MSD	1.84 (1.20-2.82)	<0.01
Age (incremental age of 10 years)	1.05 (0.95-1.16)	0.32
Year of allo-HSCT	0.96 (0.92-1.00)	0.06
RIC *versus* MAC	0.65 (0.50-0.85)	<0.01
PBSC *versus* BM	0.90 (0.68-1.18)	0.44
Female to male recipient *versus* other	1.47 (1.18-1.84)	<0.01
Patient CMV seropositivity	0.81 (0.64-1.04)	0.10
Donor CMV seropositivity	1.32 (1.03-1.69)	<0.03
Time from diagn to allo-HSCT > median	0.96 (0.91-1.01)	0.12
cGvHD		
Haplo *versus* MSD	0.75 (0.50-1.13)	0.17
Age (incremental age of 10 years)	1.10 (1.02-1.19)	<0.02
Year of allo-HSCT	1.00 (0.97-1.03)	0.99
RIC *versus* MAC	0.73 (0.60-0.89)	<0.01
PBSC *versus* BM	1.18 (0.94-1.48)	0.15
Female to male recipient *versus* other	1.48 (1.25-1.74)	<0.01
Patient CMV seropositivity	0.94 (0.78-1.12)	0.47
Donor CMV seropositivity	1.07 (0.90-1.27)	0.45
Time from diagnosis to allo-HSCT > median	1.00 (0.97-1.04)	0.7

c)	Variable	HR (95% CI) P
RI		
Haplo *versus* MSD	0.56 (0.31-1.01)	0.06
Age (incremental age of 10 years)	1.16 (1.03-1.29)	<0.02
Year of allo-HSCT	1.00 (0.95-1.05)	0.94

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RIC *versus* MAC	0.88 (0.66-1.18)	0.41
PBSC *versus* BM	0.85 (0.60-1.20)	0.36
Female to male recipient *vs.* other	0.99 (0.74-1.34)	0.97
Patient CMV seropositivity	1.19 (0.90-1.59)	0.22
Donor CMV seropositivity	0.66 (0.51-0.86)	<0.01
Time from diagnosis to allo-HSCT > median	0.95 (0.88-1.03)	0.20
NRM		
Haplo *versus* MSD	1.40 (0.62-3.13)	0.41
Age (incremental age of 10 years)	1.17 (0.95-1.43)	0.12
Year of allo-HSCT	0.88 (0.79-0.97)	0.01
RIC *versus* MAC	0.57 (0.33-0.97)	0.04
PBSC *versus* BM	0.70 (0.39-1.24)	0.22
Female to male recipient *versus* other	1.49 (0.90-2.46)	0.12
Patient CMV seropositivity	1.56 (0.87-2.77)	0.13
Donor CMV seropositivity	0.95 (0.57-1.56)	0.83
Time from diagnosis to allo-HSCT > median	1.08 (0.98-1.19)	0.11
LFS		
Haplo *versus* MSD	0.73 (0.46-1.17)	0.19
Age (incremental age of 10 years)	1.16 (1.05-1.28)	<0.01
Year of allo-HSCT	0.97 (0.93-1.02)	0.21
RIC *versus* MAC	0.80 (0.62-1.03)	0.08
PBSC *versus* BM	0.81 (0.60-1.09)	0.16
Female to male recipient *versus* other	1.11 (0.86-1.43)	0.42
Patient CMV seropositivity	1.26 (0.98-1.63)	0.07
Donor CMV seropositivity	0.72 (0.57-0.91)	<0.01
Time from diagnosis to allo-HSCT > median	0.99 (0.93-1.05)	0.80
OS		
Haplo *versus* MSD	0.73 (0.44-1.20)	0.21
Age (incremental age of 10 years)	1.19 (1.07-1.32)	<0.01
Year of allo-HSCT	0.98 (0.93-1.03)	0.38
RIC *versus* MAC	0.79 (0.60-1.02)	0.07
PBSC *versus* BM	0.82 (0.60-1.12)	0.21
Female to male recipient *versus* other	1.15 (0.88-1.51)	0.30
Patient CMV seropositivity	1.24 (0.95-1.62)	0.11
Donor CMV seropositivity	0.77 (0.60-0.98)	0.03
Time from diagnosis to allo-HSCT > median	0.99 (0.93-1.06)	0.84
GRFS		
Haplo *versus* MSD	0.88 (0.58-1.34)	0.56
Age (incremental age of 10 years)	1.09 (0.99-1.19)	0.07
Year of allo-HSCT	0.96 (0.92-1.01)	0.09
RIC *versus* MAC	0.78 (0.62-0.99)	0.04
PBSC *versus* BM	1.13 (0.85-1.51)	0.39
Female to male recipient *versus* other	1.19 (0.94-1.50)	0.14
Patient CMV seropositivity	1.05 (0.84-1.32)	0.67
Donor CMV seropositivity	0.80 (0.65-0.99)	0.04
Time from diagnosis to allo-HSCT > median	0.97 (0.92-1.03)	0.28
aGvHD II-IV		
Haplo *versus* MSD	2.20 (1.29-3.74)	<0.01
Age (incremental age of 10 years)	0.90 (0.78-1.03)	0.12
Year of allo-HSCT	0.96 (0.90-1.02)	0.22
RIC *versus* MAC	0.83 (0.56-1.21)	0.32
PBSC *versus* BM	1.30 (0.83-2.04)	0.25
Female to male recipient *versus* other	1.07 (0.73-1.55)	0.74

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Patient CMV seropositivity	0.95 (0.65-1.39)	0.80
Donor CMV seropositivity	0.94 (0.66-1.33)	0.72
Time from diagn to allo-HSCT > median	0.95 (0.87-1.04)	0.24
cGvHD		
Haplo *versus* MSD	1.02 (0.58-1.78)	0.95
Age (incremental age of 10 years)	1.07 (0.94-1.21)	0.33
Year of allo-HSCT	1.00 (0.94-1.06)	0.96
RIC *versus* MAC	0.96 (0.68-1.36)	0.83
PBSC *versus* BM	1.03 (0.68-1.56)	0.89
Female to male recipient *versus* other	1.23 (0.88-1.72)	0.23
Patient CMV seropositivity	0.87 (0.62-1.20)	0.39
Donor CMV seropositivity	1.04 (0.76-1.42)	0.79
Time from diagnosis to allo-HSCT > median	0.94 (0.87-1.03)	0.18

HR: hazard ratio; CI: confidence interval; RI: relapse incidence; NRM: non-relapse mortality; LFS: leukemia free survival; OS: overall survival; GRFS: refined graft-*versus*-host dis- ease/relapse-free survival; aGvHD: acute graft-*versus*-host disease; cGvHD: chronic graft-*versus*-host disease; Haplo: haploidentical donor; MSD: matched sibling donor; allo- HSCT: allogeneic hematopoietic stem cell transplantation; RIC: reduced intensity conditioning regimen; MAC: myeloablative conditioning regimen; PBSC: peripheral blood stem cells; BM: bone marrow; CMV: cytomegalovirus.

Propensity score matching analysis

We were able to pair-match 183 Haplo with 364 MSD. The results of propensity score analysis are summarized in Table 4.

In the group of patients presenting an intermediate risk cytogenetics, Haplo was associated with a higher risk of NRM (HR 2.59. 95% CI: 1.59-4.20. P<0.01), lower LFS (HR 1.60; 95% CI: 1.15- 2.22; P<0.01) and OS (HR 1.61; 95% CI: 1.12-2.30; P<0.01). There was no significant association between Haplo grade II-IV aGvHD, cGvHD and GRFS.

In the group of patients presenting cytogenetics classified as high risk, Haplo was associated to higher risk of acute GvHD grade II-IV (HR 2.06; 95% CI: 1.14-3.75; P=0.02) and a trend for a lower risk of relapse (HR 0.53; 95% CI: 0.28-1.01; P=0.053). There was no significant association between Haplo and other main outcomes. Survival curves according to the results of pair-matched analysis in each cytogenetic group are shown in Figure 1 and 2.

Discussion

Allogeneic HSCT might be a curative option in patients diagnosed with AML and achieving CR, especially in those with unfavorable cytogenetics for which prognosis is very poor with chemotherapy alone. Use of HSCT in patients with intermediate risk cytogenetics is sometimes debated, according to the different transplant center policies. Subsequently, for these two cytogenetic risk categories, a donor search might be immediately launched at time of diagnosis.[32] In the absence of a MSD, Haplo may represent a valid alternative, despite initial concerns being raised due to the high risk of graft failure and NRM in this setting.[9]

The aim of the current study was to compare the outcomes of patients transplanted either from a MSD or Haplo donor in patients with AML in first CR. According to cytogenetic at time of diagnosis, AML was classified as intermediate or high risk. Moreover, due to a significant interaction according to cytogenetic risk, intermediate and high-risk AML were then analyzed separately. According to donor type, higher risk of grade II-IV aGvHD was reported in Haplo recipients. Furthermore, donor CMV positive serology was found as a risk factor for aGvHD, as already shown by others.[33,34]

In agreement with previous reports,[35,36] among AML with intermediate cytogenetic risk, the intensity of the conditioning regimen was associated with higher risk of aGvHD, as well as female to male donor, while in AML with high cytogenetic risk, the only factor associated with higher risk of aGvHD was the type of donor. Furthermore, stem cell sources were not influential for acute GvHD, as previously described.[20]

No significant differences in the CI of cGvHD were found according to donor type. This could also be related to the higher proportion of BM in the Haplo group.

Our results are in some part different to those reported by Luznik *et al*.[12] Importantly, the experience reported by the Baltimore group is mainly in non myeloablative conditioning regimen and BM as stem cell source and this could in part explain the difference among our results. Also, being a registry study, we reported data from several transplant centers including different immunosuppressive protocols according to different Centers and as compared to previous reports[19] and therefore no direct comparison could be performed.

Compared with MSD recipients, Haplo recipients had a longer time to neutrophils recovery with a median time to engraftment of 2 days longer than MSD, in line with previous studies;[17,18] this is probably due to the higher proportion of patients receiving bone marrow graft among Haplos and the myelosuppression from PT-CY.

NRM was worse in the Haplo recipients in univariate and multivariate analysis. When looking at cytogenetics groups, this result was confirmed in intermediate risk, but not in high risk, where Haplo and MSD had similar NRM, in line with previous reports.[17,19,20] Furthermore, female donor to male recipient was associated to a higher NRM in intermediate AML and not in high risk AML. Therefore, one can speculate that the impact of female to male mismatch could depend on the risk of the underlying disease, as previously shown.[36] However, a possible explanation to the results in the high-risk group might be related to the low number of patients, preventing us to make definitive conclusions.

Death from infections was more common in Haplo transplants than MSD maybe due to a slower immune

Table 4. Propensity score analysis for main outcomes after allo-HSCT according to donor type in patients with intermediate (a) and high risk (b) AML.

A) Outcome	RI % ±s.d.	NRM % %±s.d.	LFS % ±s.d.	OS % ±s.d.	Gr. II-IV aGvHD %±s.d.	cGvHD% ±s.d.	GRFS% ±s.d.
Haplo	18±6	26±8	56±8	68±9	29±7	30±9	45±10
MSD	21±5	10±4	69±6	79±5	21±5	35±6	53±7
HR (95 CI)	1.04 (0.65-1.66)	2.59 (1.59-4.20)	1.60 (1.15-2.22)	1.60 (1.12-2.29)	1.49 (0.95-2.31)	0.82 (0.54-1.24)	1.27 (0.94-1.71)
P	0.86	<0.01	<0.01	<0.01	0.07	0.37	0.11

B) Outcome	RI % ±s.d.	NRM % ±s.d.	LFS % ±s.d.	OS % ±s.d.	Gr. II-IV aGvHD %±s.d.	cGvHD% ±s.d.	GRFS% ±s.d.
Haplo	22±11	17±10	61±13	67±13	37±12	37±13	51±13
MSD	39±10	13±7	48±10	57±9	21±7	31±10	41±10
HR (95 CI)	0.53 (0.28-1.00)	1.07 (0.45-2.51)	0.68 (0.40-1.13)	0.68 (0.39-1.19)	2.06 (1.13-3.74)	0.98 (0.54-1.77)	0.82 (0.52-1.28)
P	0.05	0.87	0.14	0.18	0.01	0.95	0.39

RI: relapse incidence; NRM: non-relapse mortality; LFS: leukemia-free survival; OS: overall survival; GRFS: refined graft-*versus*-host-free relapse free survival; Gr.II-IV aGvHD: grade II- IV acute graft-*versus*-host disease; cGvHD: chronic graft-*versus*-host disease; HAPLO: haploidentical donor; MSD: matched sibling donor; HR: hazard ratio; CI: confidence interval.

reconstitution in Haplo setting, also favored by the use of additional high doses of immunosuppressive agents as compared to MSD. However, as ours is a registry-based study, details on type of infections were not available.

Importantly, the type of donor did not influence the risk of relapse in intermediate AML. Recently, Ringden *et al.*[37] published no difference in leukemic relapse between MSD and Haplo. On the other hand, in high-risk AML, we found a trend for higher RI in MSD recipients; this could reflect a lower immunogenicity of MSD transplant in AML with more biological aggressive characteristics. Our results should be taken with caution as there are important factors that we were not able to take into account, and such as molecular biology data, important for disease stratification. Risk group was, indeed, defined according to cytogenetics at diagnosis.

In intermediate AML, a RIC regimen was associated to higher risk of relapse as previously described,[35] while in high-risk AML, the type of conditioning regimen affected neither relapse nor GvHD incidence In this setting, CMV serology and incremental age were the only factors affecting risk of relapse, while the type of donor was the only related to risk of GvHD.

The probability of LFS was lower in Haplo, in line with previous reports.[37]

In a retrospective study from a single center, Bashey *et al.*[17] reported outcomes of 475 patients receiving unmanipulated Haplo transplant using PT-CY in comparison to MSD or 10/10 matched unrelated donors. This series on patients with lymphoid and myeloid malignancies included 170 patients with AML. In line with our results, OS was superior in MSD as compared to Haplo recipients. Of note, they also found higher incidence of grade II-IV aGvHD, without differences in cGvHD, and higher NRM in the Haplo setting. In our study, as in Bashey population, the time from diagnosis to transplant was longer for Haplo than MSD and this could have negatively affected outcomes of transplant. In multivariate analysis, incremental age produced effects on LFS and OS, regardless of cytogenetics, in line with others.[40]

Our data were analyzed using the propensity score analysis in order to balance characteristics of the two populations. The matched pair analysis confirmed the results of higher aGvHD incidence in Haplo compared to MSD, and confirmed the main outcome results that we found in standard analysis, for both intermediate and high risk AML.

Given the main finding of our study, outcomes of transplantation from Haplo *versus* MSD depend on the leukemic cytogenetics risk. Intermediate AML outcomes were better in the MSD setting as compared to Haplo with no significant differences in RI among the two types of donor. Whilst in high-risk AML, there were no significant differences in the main transplantation outcomes between Haplo and MSD, except for the lower risk of relapse in the Haplo group. However, we acknowledge that the number of patients with high risk cytogenetics in our study was low and, consequently, the statistical power was too.

In conclusion, our results underline that matched sibling donor remain the first donor choice for AML patients in first CR when available. It should be of interest to further investigate the role of Haplo in this setting with well-designed prospective studies.

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