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Stem Cell Transplantation From a Haploidentical Donor Versus a Genoidentical Sister for Adult Male Patients With Acute Myelogenous Leukemia in First Remission: A Retrospective Study From the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation

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BACKGROUND: In adult patients with acute myeloid leukemia (AML), a matched sibling donor (MSD) is considered the first choice for an allogeneic transplantation. However, a female donor for a male recipient is a poor prognostic factor. The authors compared haploidentical (HAPLO) donors with female MSDs. **METHODS:** In total, 834 men underwent allogeneic transplantation from a female MSD, and 232 men underwent allogeneic transplantation from a HAPLO donor. Of these, 86% of HAPLO recipients and 3% of MSD recipients received graft-versus-host disease (GVHD) prophylaxis posttransplantation with high-dose cyclophosphamide. A significant qualitative interaction was observed between donor type and cytogenetics. Therefore, the analyses were stratified on cytogenetics. **RESULTS:** Of the men with intermediate-risk AML, 638 received transplantation from a female MSD, and 160 received transplantation from a HAPLO donor. In multivariate analysis, poor risk factors were a HAPLO donor versus an MSD for nonrelapse mortality (hazard ratio [HR], 1.7; $P = .02$) and patient age for nonrelapse mortality and overall survival (HR, 1.22 [$P = .02$] and 1.15 [$P = .02$], respectively). HAPLO transplantation resulted in less chronic GVHD (HR, 0.43; $P < 10^{-4}$) but lower leukemia-free survival (HR, 1.7; $P = .04$). The GVHD/relapse-free survival (GRFS) was not different. Of the men with high-risk AML, 196 received transplantation from a female MSD, and 72 received transplantation from a HAPLO donor. By multivariate analysis, HAPLO recipients had a lower incidence of relapse (HR, 0.40; $P = .004$), better leukemia-free survival (HR, 0.46; $P = .003$), better overall survival (HR, 0.43; $P = .003$), and better GRFS (HR, 0.54; $P = .006$). **CONCLUSIONS:** In men who have intermediate-risk AML, allogeneic transplantation from a sister MSD or a HAPLO donor produces similar GRFS. However, in men who have high-risk AML, a HAPLO donor combined with prophylactic high-dose cyclophosphamide posttransplantation may be a better choice. *Cancer* 2020;126:1004-1015. © 2019 American Cancer Society.

KEYWORDS: acute myeloid leukemia, haploidentical donors, matched sibling donors, stem cell transplantation.

INTRODUCTION

Since the beginning of this century, there has been considerable development and improvement in the field of allogeneic stem cell transplantation. In particular, the increasing use of peripheral blood stem cells and reduced-intensity conditioning (RIC) and the growing availability of alternative sources of stem cells have rendered allogeneic stem cell transplantation possible for almost all adult patients with acute myeloid leukemia (AML) when and if needed.¹

For most teams, whenever available, a matched sibling donor (MSD) is the first choice, and an alternative donor is considered only in the absence of an MSD.^{2,3} However, a recent retrospective study for the Center for International Blood and Marrow Transplant Research (CIBMTR)⁴ comparing haploidentical (HAPLO) versus MSD transplantation concluded that a HAPLO donor is a viable alternative to an MSD in patients who have AML in first remission (CR1).

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However, in the MSD setting, transplantation to a male recipient from a female donor using either bone marrow or peripheral blood has been associated with a higher incidence of graft-versus-host disease (GVHD), higher nonrelapse mortality (NRM), and lower leukemia-free survival (LFS) and overall survival (OS).⁵⁻⁸ Also, a joint study of Eurocord and the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT) likewise has demonstrated a higher incidence of acute GVHD (aGVHD) and lower survival in male patients transplanted with female unrelated cord blood.⁹ It was shown that this was caused at least in part by the reaction of immune female T cells to the genes present on the Y chromosome.^{10,11}

Regarding HAPLO donors and non-T-depleted grafts, there has been considerable improvement thanks to better control of GVHD as pioneered either in Baltimore,¹²⁻¹⁶ with the introduction of high-dose cyclophosphamide posttransplantation, or in Beijing,¹⁷ with the GIAC protocol combining high-dose myeloablative therapy and granulocyte colony-stimulating factor-primed bone marrow and peripheral blood, or elsewhere using other modalities.¹⁸ Several retrospective studies and a few randomized studies have shown that HAPLO transplants result in outcomes that are at least not inferior to those obtained with other alternative stem cell sources.¹⁹⁻²¹ Comparisons with umbilical cord blood in de novo²² and secondary AML²³ and with other stem cell sources in patients with relapsed/refractory Hodgkin disease and primary refractory acute AML^{20,24,25} have even favored HAPLO transplantation.

Recent studies comparing MSD with HAPLO transplantation have concluded that an MSD, when available, remains the primary choice. However, none of those studies specifically addressed the question corresponding to a clinical situation in which the available MSD for a male patient happens to be his sister. In view of the predicted higher NRM and lower LFS and OS associated with the female-to-male transplantation combination, one might question whether HAPLO transplantation would result in a similar or even better outcome. Indeed, for patients with high-risk AML, there are indications that the relapse incidence (RI) may be lower with a HAPLO donor than with an MSD.²

Currently, the impact of the donor-recipient sex combination in HAPLO transplantation is unknown: although the female donor/male recipient sex combination was recognized as a poor risk factor for outcome in the HAPLO Beijing experience,²⁶ it has been shown to have no impact on survival in a large CIBMTR

retrospective study of patients who received cyclophosphamide posttransplantation.²⁷

In the current study, we used the EBMT ALWP registry to compare male patients who had AML and underwent transplantation using an available sister MSD versus men who underwent transplantation using a HAPLO donor.

MATERIALS AND METHODS

Patients

This study was a retrospective, multicenter analysis. Data were provided by the EBMT ALWP registry. The EBMT registry is a voluntary working society comprised of greater than 550 transplantation centers that are required to report all consecutive stem cell transplantations and follow-up on an annual basis. Audits are routinely performed to ensure the accuracy of data. Since 1990, registry patients provided informed consent authorizing the use of their personal information for research purposes. The ALWP of the EBMT group approved this study.

Eligibility criteria for this analysis included male adult patients (aged ≥ 18 years; $n = 1066$) who had de novo AML reported to EBMT with available cytogenetics and Medical Research Council (MRC) classification in the intermediate-risk or high-risk group and underwent a first allograft in CR1 after a myeloablative conditioning (MAC) or RIC regimen using either a female MSD or a T-replete HAPLO male or female donor during the period from January 2007 to June 2017.

Statistical Analysis

The conditioning regimen was defined as MAC when it included total body irradiation at a dose >6 grays or a total dose of busulfan >8 mg/kg orally or >6.4 mg/kg intravenously. All other regimens were defined as RIC.²⁸ The primary endpoint was the refined GVHD/relapse-free survival (GRFS),²⁹ defined as being alive with neither grade III nor IV aGVHD, severe cGVHD, nor disease relapse at any time point. Secondary endpoints were engraftment, RI, NRM, LFS, OS, aGVHD, and chronic GVHD (cGVHD). LFS was defined as survival with no evidence of relapse or progression. Relapse was defined as the presence of 5% bone marrow blasts and/or reappearance of the underlying disease. NRM was defined as death without evidence of relapse or progression. OS was defined as the time from transplantation to death, regardless of the cause. Modified Glucksberg criteria and revised Seattle

criteria were used to grade aGVHD³⁰ and cGVHD,³¹ respectively. Engraftment was defined as achieving an absolute neutrophil count $\geq 0.5 \times 10^9/\text{L}$ for 3 consecutive days. Follow-up was estimated using a reverse Kaplan-Meier method. Patient-related, disease-related, and transplantation-related variables were compared between the 2 cohorts (MSDs/HAPLO donors) using the chi-square test or the Fisher exact test for categorical variables and the Mann-Whitney test for continuous variables. Probabilities of OS, LFS, and GRFS were calculated using the Kaplan-Meier method.³² Cumulative incidence functions were used to estimate RI and NRM in a competing risks setting.³³ 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, and the Gray test was used to determine cumulative incidence functions. Multivariate analyses adjusted for differences between the groups were performed using a Cox proportional hazards regression model.³⁴ All variables that differed significantly between the 2 groups and were not related to donor type or factors associated with 1 outcome in univariate analysis were included in the Cox model. All tests were 2-sided. The type I error rate was fixed at 0.05 for determining the factors associated with time-to-event outcomes.

All interactions between donor type and other covariates were tested, and a significant interaction according to cytogenetics was found; therefore, all analyses were stratified on the cytogenetic status at diagnosis as intermediate-risk or adverse-risk, according to the previous definition from the MRC.³⁵ Statistical analyses were performed using the SPSS (version 24.0; IBM Corporation) and R (version 3.4.0; R Development Core Team) software packages.

RESULTS

Follow-up of the entire population of patients that remained alive was 25 months (interquartile range, 2-62 months). Eight hundred thirty-four of the 1066 male patients received an MSD transplantation from a sister, and 232 received a HAPLO transplantation. HAPLO transplantations were done more recently (median year of transplantation, 2016 vs 2012; $P < 10^{-4}$), and HAPLO donors were younger than genotypical female donors (39 vs 52 years; $P < .0001$). Patients who underwent a HAPLO graft more frequently received stem cells from a bone marrow source (44% vs 16%; $P < .0001$).

Intermediate Risk Group

Table 1 shows the distribution of patients in the intermediate AML risk group. Six hundred thirty-eight patients received a graft from a genotypical sister, and 160 received a graft from a HAPLO donor. Patients (all male) who underwent transplantation from a HAPLO donor had younger donors than those who underwent transplantation from a genotypical female donor (donor age, 51 vs 39 years; $P < .0001$). The proportions who received RIC and MAC in the 2 groups were even, but the pretransplantation regimens differed. Combined busulfan and cyclophosphamide was received by 24% of patients in MSD group versus only 3% of those in the HAPLO group; conversely, the combination of thiopeta with busulfan and fludarabine (TBF) was received by 51% of patients in the HAPLO group versus only 3% of those in the MSD group. HAPLO recipients more frequently received stem cells from a bone marrow source (45% vs 17%; $P < .0001$). Prevention of GVHD also differed: 83% of patients in the HAPLO group received prophylaxis with posttransplantation high-dose cyclophosphamide (PTCY) versus only 4.6% of patients in the MSD group; in vivo T-cell depletion with antithymocyte globulin (ATG)/alemtuzumab was received by 17% of patients in the HAPLO group versus 39% of those in the MSD group.

At 2 years, genotypical sister and HAPLO donor graft recipients had a GRFS rate of 42.6% versus 42.8%, respectively ($P = .9$); a RI rate of 21.7% versus 23.4%, respectively ($P = .7$); a NRM rate of 14.7% versus 26.1%, respectively ($P = .002$); a LFS rate of 63.6% versus 50.5%, respectively ($P = .03$); and an OS rate of 69.2% versus 59.6%, respectively ($P = .08$). The rates of cGVHD (54% vs 26.5%; $P < .0001$) and severe cGVHD (26.6% vs 13.9%; $P = .002$) were significantly higher with genotypical sister donors compared with HAPLO donors in univariate analysis.

Table 2 shows results from the multivariate analysis. GRFS did not differ between HAPLO donor and MSD transplants (hazard ratio [HR], 0.94; 95% CI, 0.72-1.23; $P = .65$). HAPLO transplantation was associated with an increased NRM (HR, 1.7; 95% CI, 1.1-2.6; $P < .02$), lower LFS (HR, 1.38; 95% CI, 1.02-1.87; $P < .004$), and less cGVHD (HR, 0.43; 95% CI, 0.29-0.64; $P < 10^{-4}$). The only other significant prognostic factor was patient age (per 10 years), which negatively affected NRM (HR per 10 years, 1.22; 95% CI, 1.04-1.44; $P = .02$) and OS (HR, 1.15; 95% CI, 1.02-1.28; $P = .02$).

TABLE 1. Male Patients With Intermediate-Risk Acute Myeloid Leukemia Who Underwent Transplantation in First Remission With a Matched Sibling Donor or a Haploidentical Donor: Disease and Transplant Characteristics

Characteristic	No. of Patients (%) or Median [Range/IQR]		<i>P</i>
	Haploidentical	Female MSD	
No. of patients	160	638	
Follow-up, mo	15 [7-35]	30 [13-67]	
Patient age at transplantation, y	55 [19-74/44-64]	52 [18-73/41-60]	.007
Time from Dx to transplantation, mo	5 [2-17/4-7]	4.5 [1-15/4-6]	<.0001
Year of transplantation	2016 [2007-2017/2014-2016]	2012 [2007-2017/2009-2016]	<.0001
Donor age, y	39 [11-72/29-51]	51 [8-77/40-59]	<.0001
<i>FLT3-ITD</i> mutation	53 (49)	148 (46)	
No. missing	52	314	
<i>NMP1</i> mutation	36 (39)	118 (42)	
No. missing	68	359	
No. of inductions courses to reach CR1			
1	49 (63)	261 (72)	.1
>1	29 (37)	102 (28)	
No. missing	82	275	
Donor/recipient sex			
Male to male	91 (57)	0 (0)	
Female to male	69 (43)	638 (100)	
CMV status			
Patient CMV-positive	121 (77)	420 (67)	<.02
Donor CMV-positive	113 (72)	397 (63)	.05
Source of stem cells			
BM	72 (45)	108 (17)	<.0001
PB	88 (55)	530 (83)	
Karnofsky score			
<90%	24 (16)	131 (22)	.1
≥90%	124 (84)	454 (78)	
Conditioning regimen			
MAC	87 (54)	347 (54)	1.00
RIC	73 (46)	291 (46)	
BuCy	4 (3)	151 (24)	
BuFlu	27 (17)	218 (34)	
TBF	81 (51)	18 (3)	
FluMel	8 (5)	77 (12)	
TreoFlu	7 (4)	20 (3)	
FLAMSA	3 (2)	15 (2)	
TBI	27 (17)	121 (19)	
GVHD prevention			
In vivo T-cell depletion			
PTCY	127 (79)	17 (3)	
ATG/alemtuzumab	27 (17)	250 (39)	
Additional immunosuppression			
CSA alone	5 (3)	126 (20)	
CSA + MTX	6 (4)	322 (50)	
CSA + MMF	86 (54)	126 (20)	
MMF + TACRO	29 (18)	11 (2)	
TACRO + SIRO	0 (0)	10 (2)	
aGVGD			
Grade I	26 (17)	101 (16)	
Grade II	27 (17)	96 (15)	
Grade III	4 (3)	35 (6)	
Grade IV	8 (5)	13 (2)	
None	89 (57)	371 (60)	
No. missing	4	15	
Grade <II	115 (75)	472 (77)	.6
Grade ≥II	39 (25)	144 (23)	
No. missing	6	22	
Causes of death within 6 mo			
No. of patients	32	66	
Cardiac toxicity	2 (6)	0 (0)	
Hemorrhage	1 (3)	0 (0)	
Graft failure	0 (0)	1 (2)	

TABLE 1. *Continued*

Characteristic	No. of Patients (%) or Median [Range/IQR]		<i>P</i>
	Haploidentical	Female MSD	
VOD/SOS	1 (3)	1 (2)	
Infection	18 (58)	22 (34)	
Interstitial pneumonitis	0 (0)	1 (2)	
GVHD	4(13)	17 (26)	
Leukemia	2 (6)	19 (29)	
Second malignancy	0 (0)	0 (0)	
Other transplantation-related	3 (10)	4 (6)	
No. missing	1	1	

Abbreviations: aGVHD, acute graft-versus-host disease; ATG, antithymoglobulin; Bu, busulfan; CMV, cytomegalovirus; CR1, first complete remission; CSA, cyclosporin A; Cy, cyclophosphamide; Dx, diagnosis; FLAMSA, fludarabine, amsacrine, and cytarabine; Flu, fludarabine; GVHD, graft-versus-host disease; IQR, interquartile range; MAC, myeloablative conditioning; Mel, melphalan; MMF, mycophenolate mofetil; MTX, methotrexate; PTCY, posttransplantation high-dose cyclophosphamide; RIC, reduced-intensity conditioning; SIRO, sirolimus; TACRO, tacrolimus; TBF, thiotepa with busulfan and fludarabine; TBI, total body irradiation; Treo, treosulfan; VOD/SOS, liver veno-occlusive disease/sinusoidal obstructive syndrome.

TABLE 2. Multivariate Analysis of Prognostic Factors for Male Patients With Intermediate-Risk Acute Myeloid Leukemia

Variable	Relapse		NRM		LFS		OS	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
HAPLO vs MSD	1.13 (0.73-1.75)	.6	1.7 (1.1-2.61)	.02 ^a	1.38 (1.02-1.87)	.04 ^a	1.29 (0.92-1.82)	.14
Patient age, per 10 y	0.98 (0.86-1.12)	.8	1.22 (1.04-1.44)	.02 ^a	1.07 (0.97-1.19)	.2	1.15 (1.02-1.28)	.02 ^a
Time from diagnosis to transplantation	0.95 (0.88-1)	.2	0.96 (0.88-1.05)	.4	0.96 (0.9-1.00)	.1	0.97 (0.9-1.03)	.3
Patient CMV-positive	1.13 (0.79-1.63)	.5	0.98 (0.61-1.38)	.7	1.03 (0.79-1.36)	.8	1.04 (0.78-1.41)	.8
Donor CMV-positive	0.9 (0.64-1.28)	.6	1.27 (0.85-1.91)	.2	1.04 (0.80-1.35)	.8	1.1 (0.84-1.47)	.5
PB vs BM	0.9 (0.61-1.36)	.6	0.66 (0.43-1.00)	.05	0.78 (0.59-1.05)	.1	0.82 (0.6-1.13)	.2
RIC vs MAC	1.2 (0.83-1.73)	.3	0.97 (0.64-1.47)	.9	1.1 (0.83-1.44)	.5	1.11 (0.82-1.49)	.5

Abbreviations: BM, bone marrow; CMV, cytomegalovirus; HAPLO, haploidentical donor; HR, hazard ratio; LFS, leukemia-free survival; MAC, myeloablative conditioning; MSD, matched sibling donor; NRM, nonrelapse mortality; PB, peripheral blood; RIC, reduced-intensity conditioning.

^aThese *P* values indicate a significant difference.

Figure 1 shows the outcome posttransplant with a genoidentical sister or a HAPLO donor. The GRFS curves are superimposable.

High-Risk Group

Table 3 shows the distribution of patients in the high-risk group. One hundred ninety-six patients received a graft from a genoidentical sister, and 72 received a graft from a HAPLO donor. Patients (all male) who received grafts from a HAPLO donor had younger donors than those who received grafts from a genoidentical female donor (donor age, 38 vs 54 years; $P < .0001$). The proportions of RIC and MAC in the 2 groups were similar, but the pretransplantation regimens were heterogeneous and differed: for example, TBF was received by 43% of patients of the HAPLO group versus only 4% of those in the MSD group, whereas busulfan and cyclophosphamide was received by 19% of patients in the MSD group but by none of those in HAPLO group. The HAPLO group more frequently received stem cells from a bone marrow source (42% vs 11%; $P < .0001$). Prevention of GVHD also differed: 92% of patients in the HAPLO group received PTCY versus only

3% of those in the MSD group; in vivo T-cell depletion with ATG/alemtuzumab was used in 20% of patients in the HAPLO group versus 39% of those in the MSD group.

At 2 years, genoidentical sister and HAPLO donor graft recipients had a GRFS rate of 25.9% versus 52.1%, respectively ($P = .001$); an RI rate of 47.1% versus 24.5%, respectively ($P = .003$); an NRM rate of 14.7% versus 13%, respectively ($P = .8$); an LFS rate of 38.3% versus 62.4%, respectively ($P = .003$); and an OS rate of 41.9% versus 68.5%, respectively ($P = .006$). For genoidentical sister and HAPLO donor graft recipients, the rates of aGVHD scores of III and IV (7.4% vs 4.2%, respectively; $P = .48$), cGVHD (40% vs 39%, respectively; $P = .62$), and severe cGVHD (20.7% vs 12.7%, respectively; $P = .17$) were not significantly different in univariate analysis.

Table 4 shows results from the multivariate analysis. HAPLO transplants were associated with better GRFS (HR, 0.54; 95% CI, 0.34-0.84; $P = .006$), lower RI (HR, 0.40; 95% CI, 0.21-0.75; $P = .004$), better LFS (HR, 0.46; 95% CI, 0.28-0.77; $P = .002$), and better OS (HR, 0.43; 95% CI, 0.25-0.75; $P = .003$). The only

Figure 1. (A-F) Charts illustrate the outcomes of adult male patients with intermediate-risk acute myeloid leukemia in first complete remission who underwent allogeneic transplantation with stem cells from a genoidentical sister or a haploidentical (Haplo) donor. cGVHD indicates chronic graft-versus-host disease; GRFS, graft-versus-host disease relapse-free survival; MSD, matched sibling donor; NRM, nonrelapse mortality.

other significant prognostic factor was patient age, which negatively affected NRM (HR per 10 years, 1.55; 95% CI, 1.09-2.21; $P = .014$), LFS (HR, 1.22; 95% CI, 1.03-1.44; $P = .02$), and OS (HR, 1.32; 95% CI, 1.1-1.6; $P = .002$). There was no difference in outcomes in the HAPLO group according to whether the sex of the donor was male or female.

Figure 2 illustrates the posttransplantation outcomes of patients who received grafts from a sister MSD or a HAPLO donor. The GRFS after transplantation from a

HAPLO donor was superior to the GRFS after transplantation from a sister MSD.

Donor Sex in Recipients of HAPLO Transplantation

We studied the 2 combinations of a female donor to a male recipient and a male donor to a male recipient in the entire population of HAPLO recipients and separately in the intermediate-risk and adverse-risk groups (see Supporting Table 1). In the entire HAPLO population of

TABLE 3. Male Patients With High-Risk Acute Myeloid Leukemia who Underwent Transplantation in First Remission With a Matched Sibling Donor or a Haploidentical Donor: Disease and Transplant Characteristics

Characteristic	No. of Patients (%) or Median [Range/IQR]		<i>P</i>
	Haploidentical Donor	Female MSD	
No. of patients	72	196	
Follow-up, mo	16 [9-35]	31 [12-64]	
Patient age at transplant, y	54 [18-75/39-61]	55 [19-72/44-61]	.6
Time from Dx to transplantation, mo	5 [1-16/4-6]	4 [2-14/3-5]	.003
Year of transplantation	2016 [2009-2017/2014-2016]	2013 [2007-2017/2011-2016]	<.0001
Donor age, y	38 [18-75/27-49]	53 [13-72/44-60]	<.0001
<i>FLT3-ITD</i> mutation	6 (15.38)	11 (15.07)	.96
<i>NPM1</i> mutation	0 (0.0)	8 (12.12)	.05
No. of induction courses to reach CR1			
1	24 (67)	74 (70)	.7
>1	12 (33)	32 (30)	
Donor sex			
Male	42 (58)	0 (0)	<.0001
Female	30 (42)	196 (100)	
CMV status			
Patient CMV-positive	55 (76)	124 (64)	.05
Donor CMV-positive	46 (65)	131 (68)	.6
Source of stem cells			
BM	30 (42)	22 (11)	<.0001
PB	42 (58)	174 (89)	
Karnofsky score			
<90%	16 (24)	36 (20)	.5
≥90%	50 (76)	142 (80)	
Conditioning regimen			
MAC	33 (46)	102 (52)	.4
RIC	39 (54)	94 (48)	
BuCy	0 (0)	37 (19)	
BuFlu	8 (11)	61 (31)	
TBF	31 (43)	8 (4)	
FluMel	2 (3)	17 (9)	
TreoFlu	4 (6)	10 (5)	
FLAMSA	3 (4)	15 (8)	
TBI	23 (32)	44 (22)	
GVHD prevention			
In vivo T-cell depletion			
PTCY	66 (92)	6 (3)	
ATG/alemtuzumab	15 (20)	77 (39)	
Additional immunosuppression			
CSA alone	2 (3)	35 (18)	
CSA + MTX	2 (3)	82 (42)	
CSA + MMF	36 (50)	59 (30)	
MMF + TACRO	25 (35)	8 (4)	
TACRO + SIRO	3 (4)	0 (0)	
aGVHD			
Grade I	10 (14)	27 (14)	
Grade II	15 (21)	30 (16)	
Grade III	2 (3)	11 (6)	
Grade IV	2 (2.8)	5 (2.6)	
No aGVHD	42 (58)	117 (61)	
aGVHD grade <II	52 (73)	144 (76)	.7
aGVHD grade ≥II	19 (27)	46 (24)	
Causes of death within 6 mo			
No. of patients	9	33	
Cardiac toxicity	0 (0)	0 (0)	
Hemorrhage	1 (13)	1 (3)	
VOD	0 (0)	0 (0)	
Infection	3 (38)	7 (21)	
Interstitial pneumonitis	0 (0)	3 (9)	
GVHD	0 (0)	7 (21)	
Leukemia	2 (25)	14 (42)	
Second malignancy	0 (0)	0 (0)	
Other transplantation-related	2 (25)	1 (3)	

Abbreviations: aGVHD, acute graft-versus-host disease; ATG, antithymoglobulin; Bu, busulfan; CMV, cytomegalovirus; CR1, first complete remission; CSA, cyclosporin A; Cy, cyclophosphamide; Dx, diagnosis; FLAMSA, fludarabine, amsacrine, and cytarabine; Flu, fludarabine; GVHD, graft-versus-host disease; IQR, interquartile range; MAC, myeloablative conditioning; Mel, melphalan; MMF, mycophenolate mofetil; MTX, methotrexate; PTCY, posttransplantation high-dose cyclophosphamide; RIC, reduced-intensity conditioning; SIRO, sirolimus; TACRO, tacrolimus; TBF, thiotepea with busulfan and fludarabine; TBI, total body irradiation; Treo, treosulfan; VOD/SOS, liver veno-occlusive disease/sinusoidal obstructive syndrome.

TABLE 4. Multivariate Analysis of Prognostic Factors for Male Patients With High-Risk Acute Myeloid Leukemia

Variable	Relapse		NRM		LFS	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
HAPLO vs MSD	0.40 (0.21-0.75)	.005 ^a	0.58 (0.23-1.43)	.24	0.46 (0.28-0.77)	.003 ^a
Patient age, per 10 y	1.11 (0.92-1.35)	.3	1.55 (1.09-2.21)	.02 ^a	1.22 (1.03-1.44)	.02 ^a
Time from diagnosis to transplantation	0.95 (0.84-1.07)	.4	1.09 (0.96-1.25)	.2	1.00 (0.92-1.1)	.96
Patient CMV-positive	1 (0.65-1.53)	1.00	1.88 (0.8-4.41)	.2	1.15 (0.79-1.68)	.46
Donor CMV-positive	0.66 (0.44-1)	.05	1.37 (0.6-3.14)	.5	0.79 (0.55-1.14)	.2
PB vs BM	0.84 (0.48-1.48)	.6	0.96 (0.38-2.39)	.9	0.89 (0.55-1.44)	.6
RIC vs MAC	0.8 (0.5-1.29)	.4	0.48 (0.22-1.02)	.06	0.68 (0.45-1.02)	.06

Abbreviations: BM, bone marrow; CMV, cytomegalovirus; HAPLO, haploidentical; HR, hazard ratio; LFS, leukemia-free survival; MAC, myeloablative conditioning; MSD, matched sibling donor; NRM, nonrelapse mortality; PB, peripheral blood; RIC, reduced-intensity conditioning.

^aThese *P* values indicate a significant difference.

232 recipients, there was no significant difference in any outcome parameter (including RI), except for extensive cGVHD, in which the incidence was 20.3% in the female-to-male combination versus only 7.5% in the male-to-male combination (univariate *P* = .015). The GRFS rates for the female-to-male and male-to-male combinations were 38% and 52.5%, respectively, at 2 years, but without statistical significance. In both the intermediate-risk and high-risk groups, there was no statistically significant difference in the outcomes of HAPLO recipients whether the sex of the donor was male or female.

DISCUSSION

For decades, allogeneic stem cell transplantation has been restricted to patients with genotypical siblings until alternative donors became an option for those without a matched identical sibling. The use of nongenotypical family donors has for long been unsuccessful. The Perugia team pioneered the field by demonstrating the possibility of using HAPLO family donors by combining T-cell depletion with the infusion of megadose selected CD34-positive cells.³⁶ In the past decade, a major improvement occurred with the introduction in Baltimore of high-dose cyclophosphamide¹²⁻¹⁴ immediately after transplantation (PTCY) to prevent GVHD and the development in Beijing of the GIAC protocol,^{17,37} which used a myeloablative regimen with ATG and a combination of granulocyte colony-stimulating factor-mobilized peripheral blood and bone marrow stem cells.

In Europe, the Baltimore approach has been used by the majority of teams, and the HAPLO approach has rapidly emerged as a principal alternative for patients who lack HLA-matched related or unrelated donors.^{18,19,38,39} The number of HAPLO transplantations has rapidly increased given near-universal donor availability, the low cost of graft acquisition, logistical simplicity, and a

reduced incidence of aGVHD and cGVHD, including severe cGVHD, despite specific complications such as cardiac failure and hemorrhagic cystitis related to high-dose cyclophosphamide.⁴⁰⁻⁴²

Several retrospective studies have reported similar outcomes of PTCY transplantations in 10 of 10 or 9 of 10 matched unrelated donors.^{19,20,43} Other have reported better results with HAPLO donors compared with umbilical cord blood in patients with de novo AML and in those with secondary leukemias.^{22,23} In patients with relapsed/refractory Hodgkin disease, HAPLO transplantation has been credited for offering the most potent antitumor effect.^{25,44} The EBMT ALWP has recently proposed consensus recommendations for clinical applications of donor lymphocyte infusions from HAPLO donors and has recommended its use as safe and effective in patients in relapse or who still have detectable MRD and/or mixed donor chimerism after a HAPLO transplantation.⁴⁵ For many teams, HAPLO donors are becoming the first choice when an alternative donor is sought. The question whether a HAPLO donor might produce outcomes similar to those produced by genotypical donors has recently been investigated retrospectively by the EBMT in a matched-pair analysis of 2654 adult patients with intermediate-risk and high-risk leukemia.² In a multivariate analysis of patients with intermediate-risk disease, the use of MSDs was associated with higher LFS, OS, and GRFS and with lower GVHD-related NRM. However, in contrast in patients with high-risk AML, the results from HAPLO donors were similar to those from genotypical donors and included a trend toward lower RI. In a CIBMTR retrospective study in patients who underwent transplantation for AML in CR1, 336 who underwent a PTCY-based HAPLO transplantation were compared with 869 who underwent an MSD

Figure 2. (A-F) Charts illustrate the outcomes of adult male patients with high-risk acute myeloid leukemia in first complete remission who underwent allogeneic transplantation with stem cells from a genoidentical sister or a haploidentical (Haplo) donor. cGVHD indicates chronic graft-versus-host disease; GFRS, graft-versus-host disease relapse-free survival; MSD, matched sibling donor; NRM, nonrelapse mortality.

transplantation using calcineurin GVHD prevention. The HAPLO group had a significantly lower incidence of cGVHD but had similar other outcomes, leading to the conclusion that a HAPLO transplantation with PTCY was a viable alternative to MSD transplantation in this patient population.⁴ Finally, in a recent joint EBMT-CIBMTR study, patient age appeared to be important, with equivalent outcomes reported using MSDs or HAPLO donors in patients aged <55 years, but with better outcomes using MSDs in older patients.⁴⁶

In view of these results, we considered a practical possible clinical issue: ie, what would be the best choice for transplantation in a male patient with intermediate-risk or high-risk AML who has a unique genoidentical sister available. We wondered whether, in this situation, we should still advocate in favor of the sister MSD or also might consider an (albeit counterintuitive) HAPLO family donor. The current study in male patients with intermediate-risk AML demonstrated that the choice of a female MSD for a male recipient was associated with lower NRM

and better LFS but, interestingly, that GRFS was similar to that of HAPLO recipients because HAPLO transplantation resulted in less cGVHD.

An important aspect to consider in our intermediate-risk group was the unexpectedly high NRM of 26% observed post-HAPLO transplantation. Not only was this superior to female MSD transplantation in this group (15%), but it also was higher than that in the HAPLO high-risk group (13%). This was also substantially higher than the NRM reported by the CIBMTR registry,¹⁹ which reported only 14% at 3 years for HAPLO recipients who received MAC and 9% for those who received RIC. Conversely, this NRM among patients who were in CR1 after HAPLO transplantation almost reached the NRM of 31% reported recently by the EBMT,³ although those patients had advanced leukemia and underwent transplantation for active disease. When considering only the 79% of our intermediate risk patients that received PTCY for GVHD prophylaxis, the NRM still remained at a similar level of 24.6% (95% CI, 16.2%-33.8%).

This is an important point because, in the absence of such a high NRM, HAPLO transplantation, which currently produces a GRFS similar to that produced by transplantation from a female MSD, would probably result at least in a similar LFS. Clearly, at the moment, the NRM reported post-HAPLO by the EBMT is higher than that reported by the CIBMTR.

Such differences may be associated with unmeasured confounding factors related to patient characteristics or to center-specific strategies that are not reported to the registries. Further studies comparing female MSDs with HAPLO donors appear to be warranted.

In contrast to intermediate-risk patients, in those with high-risk disease, HAPLO transplantation unquestionably was associated with a lower RI, better LFS, better OS, and better GRFS. Our finding of a lower relapse rate post-HAPLO in the adverse-risk group is new. In particular, Ringden et al⁴⁷ studied 10,679 patients with acute leukemia patients, of whom 9815 underwent MSD transplantation and 864 underwent HAPLO transplantation in the earlier period from 2007 and 2012. Those authors reported a similar risk of relapse after HAPLO and MSD transplantation, suggesting a similar graft-versus-leukemia (GVL) effect. In their study, however, the population of patients included both AML and acute lymphocytic leukemia together with all stages of disease, and there was a higher proportion of patients with advanced disease in the HAPLO donor group compared with the MSD group; the authors themselves acknowledged that the HAPLO group had an inherent overall higher probability

of relapse. Cytogenetics were missing for the majority of patients, and the study was not stratified by cytogenetic risk groups. The HAPLO group contained only 88 men, of whom only 48 had available cytogenetics; there were only 7 male patients in the adverse-risk group, and there was no dedicated study of the female-to-male MSD sex combination.

Our current study is different in many aspects: first, it covered the period from 2007 to 2017 and thus includes patients who underwent transplantation more recently. Also, as indicated above, it concerned only patients who had AML in CR1, all of whom had available cytogenetics. All interactions between donor type and other covariates were tested. Because we found a significant interaction according to cytogenetics, all analyses were stratified on the cytogenetic status at diagnosis in those with intermediate-risk or adverse-risk disease, according to the previous definition from the MRC.

The more recent study from the EBMT² of patients who underwent transplantation from 2007 to 2015 compared MSDs with HAPLO donors in recipients who had AML in CR1. That group reported similar outcomes in patients with adverse-risk cytogenetics. However, there was a trend in favor of a lower RI post-HAPLO transplantation (HR, 0.56; 95% CI, 0.31-1.01; $P = .06$). In part, it is because of findings from that study that we wondered whether HAPLO transplantation might produce a significantly better outcome than MSD transplantation in a recognized unfavorable MSD situation, ie, with a sister MSD.

Therefore, our current study completes the previous study in patients with AML who underwent transplantation in CR1 by showing that the trend observed in favor of HAPLO donors in high-risk patients² now appears to be significant when studying male patients who undergo transplantation from a sister MSD and not an identical brother.

The CIBMTR study,⁴ which compared outcomes between 869 patients with AML in CR1 who underwent transplantation from an MSD and 336 patients who underwent PTCY HAPLO transplantation, had similar outcomes. However, that study did not address the question we raised in our own study; ie, male recipients receiving sister MSD versus HAPLO transplantation stratified by cytogenetics.

The reasons why the RI was lower in high-risk patients post-HAPLO are uncertain. We first looked at the incidence of GVHD, but we did not find any difference in the cytogenetic adverse-risk group in the rate of aGVHD and cGVHD post-HAPLO transplantation that might account for an increased GVL effect. This indeed

confirms a recent EBMT study showing the absence of an association between GVL and GVHD post-HAPLO transplantation.⁴⁸

There were some differences of potential importance between HAPLO and sister MSD transplantations: HAPLO transplantations were done more recently. The conditioning regimen pretransplantation differed: approximately 50% of patients in the HAPLO group received the TBF combination favored in Europe versus only 3% of those in the MSD group. There was an impact of donor sex in the overall HAPLO group, with a significant increase in extensive cGVHD for female donors versus male donors, but the proportion of female donors for HAPLO recipients in the intermediate-risk and adverse-risk group was similar (57% and 58%, respectively); unfortunately, we had no information on the number of pregnancies in the female donors, which might be important in terms of immunization. This is key information that is currently sought for the next EBMT HAPLO survey.

In the end, the explanation for why HAPLO transplantations resulted in better outcomes for patients with high-risk AML may combine several cumulative factors, such as the HAPLO stem cell source (which, in addition to being mismatched, was from bone marrow in 42% vs 11% in the MSD group) and the use of PTCY, among others. This finding supports a dissociated effect with a reduction in GVHD without abrogation of GVL, as found previously by Shimoni et al.⁴⁸

Whatever the explanation, it is important to remember that, in fact, our study has not compared 2 different stem cell sources but, rather, 2 different stem cell transplantation strategies over 2 different time periods, during which the best and unique available donor has been used with no alternative choice.

High-dose cyclophosphamide is currently being tested in several institutions for GVHD prevention in matched unrelated donor and MSD transplantations.⁴⁶ It seems reasonable to speculate that PTCY in MSD transplantations may erase the “female donor to male recipient” combination recognized as a poor-risk prognostic factor, thereby establishing a MSD definitively as a reasonable intuitive first choice in all situations, but this remains to be demonstrated in prospective studies. Currently, a HAPLO family donor with the use of posttransplantation high-dose cyclophosphamide may be a better choice than a sister MSD for male patients with high-risk AML. Furthermore, although the study was neither designed for nor powered enough to study the effects of the sex, age, and female parity of the HAPLO donors, these factors also could be considered in the choice of a donor in some specific clinical situations.

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AUTHOR CONTRIBUTIONS

Norbert-Claude Gorin: Principal investigator, conceptualization, writing—original draft, and writing—revisions. **Myriam Labopin:** Conceptualization, statistical methods, and conducted the study. **Didier Blaise, Marco de Groot, Gerard Socié, Jean Henri Bourhis, Fabio Ciceri, Emmanuelle Polge, Arnon Nagler, Mohamad Mohty:** Members of the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation, provided data for analysis, approved the study synopsis, reviewed and edited the original article, and approved the final version.

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