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Haploidentical

Mother Donors Improve Outcomes after HLA Haploidentical Transplantation: A Study by the Cellular Therapy and Immunobiology Working Party of the European Society for Blood and Marrow Transplantation

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A B S T R A C T

Transplacental trafficking of maternal and fetal cells during pregnancy establishes long-term reciprocal microchimerism in both mother and child. Consequently, the maternal immune system may become sensitized to paternal histocompatibility antigens. It has been hypothesized that mother's "exposure" to paternal HLA haplotype antigens during pregnancy may affect the outcome of hematopoietic stem cell transplantation (HSCT) when the mother serves as a donor for the child. In T cell-depleted HLA haploidentical HSCT, maternal donors have been associated with improved transplantation outcomes. The present retrospective multicenter study, conducted on behalf of the Cellular Therapy and Immunobiology Working Party of the European Society of Blood and Marrow Transplantation, involved 409 patients (102 pediatric and 307 adult) with acute leukemia who underwent HLA-haploidentical HSCT. The goal of the study was to evaluate the role of maternal donors in a large cohort of haploidentical transplantation recipients. Transplantation from maternal donors was associated with a lower relapse incidence in T cell-depleted HSCTs (hazard ratio [HR], 2.13; 95% confidence interval [CI], 1.16 to 3.92; $P = .018$) as well as in a limited series of unmanipulated in vivo T cell-depleted HSCTs (HR, 4.15; 95% CI, 0.94 to 18.35; $P = .06$), along with better graft-versus-host disease/relapse-free survival (GRFS) in T cell-depleted HSCT (HR, 1.67; 95% CI, 1.02 to 2.73; $P = .04$). These results indicate that the mother is the preferred donor to provide better GRFS in T cell-depleted HLA-haploidentical HSCT for acute leukemia.

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is potentially able to eradicate high-risk acute leukemia. The best results have been obtained with HLA- matched related or unrelated donors. More recently, HSCT from full HLA

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haplotype-mismatched (ie, haploidentical) related donors has become a viable alternative option [1]. In a search for features able to positively impact the outcomes of haploidentical HSCT, we considered the transplacental trafficking of maternal and fetal cells during pregnancy. The consequent long-term reciprocal microchimerism in both mother and child may sensitize the maternal immune system against the paternal HLA haplotype [2–5].

Antibodies directed against paternal HLA antigens [6] and T lymphocytes directed against paternal major and minor histocompatibility antigens have been detected in multiparous women [7]. Stern et al. [8] previously reported improved survival after T cell-depleted haploidentical HSCT using maternal donors (compared with all other family members) [8]. Here we present results of a multicenter retrospective study performed by the Cellular Therapy and Immunobiology Working Party of the European Society of Blood and Marrow Transplantation (EBMT). The study was conducted in a cohort of 409 patients, including recipients of haploidentical HSCT performed with ex vivo T cell-depleted as well as unmanipulated (ie, in vivo T cell-depleted) grafts. Our findings indicate that transplantation from maternal donors (compared with all other family members) is associated with a lower incidence of leukemia relapse in both in vivo and ex vivo T cell-depleted haploidentical HSCT, as well as better extensive graft-versus-host disease (GVHD)/relapse-free survival (GRFS) in ex vivo T cell-depleted HSCT.

METHODS

Patients

This multicenter EBMT registry-based study was carried out in accordance with EBMT guidelines for retrospective studies. The EBMT is a nonprofit scientific society representing more than 600 transplantation centers located mainly in Europe that are required to report all consecutive stem cell transplantations and follow-ups annually. Data are entered, managed, and maintained in a central database with Internet access; each EBMT center is represented in this database. Audits are performed on an annual basis to verify the accuracy of the data. Eight EBMT centers participated in the present study.

The study was performed in a series of 409 patients who underwent HSCT from a haploidentical family donor between January 1995 and June 2012. Inclusion criteria were as follows: (1) adult and pediatric patients; (2) diagnosis of acute myelogenous leukemia (AML) or acute lymphoblastic leukemia (ALL); (3) transplantation from an HLA-haploidentical related donor; (3) bone marrow and/or GCS-F-mobilized peripheral blood stem cells as the hematopoietic stem cell source; and (4) GVHD prophylaxis with pharmacologic immunosuppression including in vivo T cell depletion (TCD) (mostly with antithymocyte globulin [ATG]) or ex vivo TCD.

All patients provided informed consent authorizing the use of their personal information for research purposes. The Cellular Therapy and Immunobiology Working Party of the EBMT and the EBMT Board approved this study.

Endpoints and Definitions

The primary study endpoints were incidences of acute GVHD (aGVHD) and chronic GVHD (cGVHD), relapse, nonrelapse mortality (NRM), and probabilities of progression-free survival (PFS) and GRFS. NRM was defined as death without previous evidence of relapse or progression. PFS was defined as survival without prior disease relapse/progression or death from any cause. GRFS was defined as survival without prior occurrence of either relapse/progression or grade III-IV aGVHD or extensive cGVHD (the term "extensive cGVHD" rather than the standard cGVHD requiring systemic immunosuppression is used, because cGVHD immunosuppressive treatments were not available for all patients). All outcomes were measured since the time of HSCT.

Statistics

Categorical risk factors were summarized by frequency and percentage, and group differences were analyzed using the chi-square test. Continuous risk factors were summarized by median with range or interquartile range, with group differences analyzed using the *t* test. Probabilities of overall survival, PFS, and GRFS were estimated by the Kaplan-Meier method, and the log-rank test was used for univariate comparisons of subgroups. Median follow-up was calculated according to the reverse Kaplan-Meier method. Competing-risk analyses were separately applied to estimate the incidences of aGVHD, extensive cGVHD, neutrophil and platelet engraftment, relapse/progression, and NRM. The competing risks for aGVHD and extensive cGVHD were graft failure, post-transplantation delayed donor lymphocyte infusion, and second HSCT. All other competing-risk analyses considered death as the sole competing event. The cumulative incidence of aGVHD was evaluated at day +100 post-transplantation, and cGVHD, relapse, and NRM were evaluated at 5 years post-transplantation. Subgroup differences in cumulative incidence were analyzed using Gray's test. Multivariable Cox regression was applied to investigate the simultaneous impact of multiple covariates on PFS and GRFS. Covariates included family relation (other donors versus mother donor), graft manipulation (ex vivo T cell-depleted graft versus unmanipulated graft), sex, Karnofsky Performance Status (KFS) (<90 versus 90 to 100), disease (ALL versus AML), stem cell source (peripheral blood stem cells versus bone marrow), recipient cytomegalovirus serostatus, age in decades, time from diagnosis to transplantation in months, and disease stage at transplantation (no complete remission [CR] versus CR). In addition, the effects of the donor in T cell-depleted and unmanipulated transplants were investigated by means of interactions between donor relation and ex vivo TCD, adjusted for the covariates mentioned earlier. A further subgroup analysis of transplantation outcomes was performed in patients age <25 years. Unadjusted univariate analyses of NRM, relapse, PFS, and GRFS were performed in patients grouped according to whether they had received their transplant from a maternal donor versus all other family members. Owing to the low numbers of patients and events in these subgroups, propensity score adjustment by quintile stratification was performed to estimate the adjusted effects of donor relation. A logistic regression model was used to estimate the probability of having received a donor graft from the mother, including covariates, ex vivo and in vivo TCD, patient sex, KPS, age at transplantation, stem cell source, diagnosis, disease status at transplantation, interval between diagnosis and transplantation, and patient cytomegalovirus serostatus. The propensity scores were categorized in 5 balanced groups which were used to stratify Cox cause-specific hazard models of PFS, GRFS, and relapse. All estimates are reported with corresponding 95% confidence intervals (CI), and $P < .05$ was considered statistically significant (2-sided). All analyses were performed using R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) with the survival, prodlim, and cmprsk packages.

RESULTS

The study cohort comprised 151 patients with ALL and 258 with AML. Patient characteristics are presented in Table 1. Two hundred and twenty-two patients (54.5%) underwent transplantation while in complete remission (CR). The median age at HSCT was 32.6 years (range, 0.7 to 70 years). The conditioning regimen was based on sublethal (2 to 4 Gy) total body irradiation (TBI) in 49 patients, lethal (7 to 13 Gy) TBI in 207 patients, or a chemotherapy-based conditioning regimen composed of busulfan or treosulfan and fludarabine and ATG or anti-CD3 in 146 patients. In 168 patients, lethal TBI was combined with fludarabine, thiotepa and ATG. Two hundred and ninety-six patients (72.7%) received ex vivo T cell-depleted transplants. Two hundred and thirty-eight grafts were T cell depleted by positive selection of $CD34^+$ hematopoietic stem cells, 43 grafts were T cell depleted by negative selection of T and B cells, and 13 grafts were T cell depleted by both selection procedures. One hundred and eleven patients (27.3%) received an unmanipulated transplant (all obtained from leukapheresis products). Pharmacologic GVHD prophylaxis was provided with ATG, sirolimus, and mycophenolate mofetil.

The mother served as the donor in 96 transplantations (23.5%), of which 79 were T cell depleted and 16 were unmanipulated. The median duration of follow-up was 67.6 months (range, 64.9 to 72.9 months). The day +100 incidence of neutrophil engraftment was 95% (95% CI, 93% to 97%). The median time to neutrophil engraftment was 14 days (range, 13 to 15 days). The day +100 cumulative incidence of grade II-IV aGVHD was 15% (95% CI, 12% to 19%), and the cumulative incidence of extensive cGVHD at 60 months was 6% (95% CI, 3% to 8%). At the 60-month follow up, 26% of the patients (95% CI, 22% to 31%) were alive without disease, 39% (95% CI, 34% to 44%) had relapsed, and 35% (95% CI, 30% to 40%) had died of NRM.

We then compared the outcomes of haploidentical HSCT from maternal donors with outcomes of haploidentical HSCT from all other family donors. Because the outcomes from

Table 1
Patient Demographics, Overall and Stratified by Donor Relation (Mother versus all Other Family Members)

Variable		Missing, n (%)	Total	Mother to Child	Other	*P*
Donor			409 (100)	96 (23.5)	313 (76.5)	
Disease, n (%)	AML		258 (63.1)	43 (44.8)	215 (68.7)	<.001
	ALL		151 (36.9)	53 (55.2)	98 (31.3)	
Status, n (%)	CR	2 (0.5)	222 (54.5)	56 (58.9)	166 (53.2)	.4
	No CR		185 (45.5)	39 (41.1)	146 (46.8)	
Patient age, yr	Median (range)		32.6 (0.7-70)	15.9 (0.7-50.8)	38.5 (1.5-70)	<.001
Sex, n (%)	Male		224 (54.8)	53 (55.2)	171 (54.6)	>.99
	Female		185 (45.2)	43 (44.8)	142 (45.4)	
KPS, n (%)	<90	22 (5.4)	71 (18.3)	11 (13.3)	60 (19.7)	.2
	90-100		316 (81.7)	72 (86.7)	244 (80.3)	
In vivo TCD, n (%)	No	55 (13.4)	50 (14.1)	15 (17.4)	35 (13.1)	.4
	Yes		304 (85.9)	71 (82.6)	233 (86.9)	
Ex vivo TCD, n (%)	No	2 (0.5)	111 (27.3)	16 (16.8)	95 (30.4)	.013
	Yes		296 (72.7)	79 (83.2)	217 (69.6)	
Graft source, n (%)	BM	1 (0.2)	21 (5.1)	7 (7.3)	14 (4.5)	.4
	PBSCs		387 (94.9)	89 (92.7)	298 (95.5)	
Patient CMV serostatus, n (%)	Negative	2 (0.5)	70 (17.2)	26 (27.4)	44 (14.1)	.004
	Positive		337 (82.8)	69 (72.6)	268 (85.9)	
Donor CMV serostatus, n (%)	Negative	2 (0.5)	80 (19.7)	16 (16.8)	64 (20.5)	.5
	Positive		327 (80.3)	79 (83.2)	248 (79.5)	
Donor age, yr	Median (range)	82 (20)	37.3 (14.2-71.2)	45.3 (20.6-71.2)	35.1 (14.2-69.7)	<.001
Year of transplantation	Median (IQR)		2006 (2002-2009)	2007 (2002.8-2010)	2006 (2002-2009)	.4
Time from diagnosis to HSCT, mo	Median (IQR)		11.9 (7.1-22.8)	14.6 (8.2-29.1)	11 (6.4-20.6)	.3

P values of comparisons of categorical risk factors are based on the chi-square test, and *P* values of comparisons involving continuous risk factors are based on the *t* test.
CMV indicates cytomegalovirus; IQR, interquartile range.

family donors other than mothers did not differ from one another (as shown by univariable analyses; multivariable analyses could not be applied owing to the small sizes of these individual groups), all other family donor HSCTs were combined for analysis (Supplementary Table S1). By 100 days and 60 months respectively, the incidences of aGVHD and extensive cGVHD were similar in recipients of HSCT from maternal donors (n = 96) and recipients of HSCT from all other family donors (n = 313) (aGVHD: 17% (95% CI, 9% to 24%) and 15% (95% CI, 11% to 19%), respectively; extensive cGVHD: 6% (95% CI, 1% to 12%) and 6% (95% CI, 3% to 8%), respectively (Figure 1A and B). Interestingly, haploidentical HSCT from maternal donors was associated with lower incidence of relapse (30% [95% CI, 21% to 40%] versus 41% [95% CI, 36% to 47%]; $P = .07$) (Figure 1C), lower incidence of NRM (28% [95% CI, 19% to 37%] versus 37% [95% CI, 32% to 43%]; $P = .15$) (Figure 1D), better PFS (42% [95% CI, 32% to 52%] versus 21% [95% CI, 16% to 26%]; $P = .002$), and better GRFS (38% [95% CI, 27% to 48%] versus 15% [95% CI, 11% to 20%]; $P < .001$) (Figure 1E and F). Univariate analyses identified that maternal donor, younger patient age, CR at transplantation, KPS >90, and ex vivo TCD positively influenced PFS (Table 2). Multivariable analyses showed that HSCT from nonmaternal donors was predictive of higher relapse incidence (hazard ratio [HR], 2.16; 95% CI, 1.23 to 3.77; $P = .007$), worse PFS (HR, 1.63; 95% CI, 1.1 to 2.41; $P = .015$), and worse GRFS (HR, 1.57; 95% CI, 1.04 to 2.37; $P = .033$) (Table 3). In addition, a comparison of outcomes of HSCT in male recipients from mother donors versus nonmother female donors (including, eg, female sibling to male sibling and daughter to father) showed better PFS and better GRFS from the mother donors (PFS: 42% [95% CI, 32% to 52%] versus 25% [95% CI, 13% to 37%], $P = .08$; GRFS: 38% [95% CI, 27%-48%] versus 20% [95% CI, 8% to 31%], $P = .08$). Comparisons between mother-to-daughter HSCT and mother-to-son HSCT did not show any differences. Comparisons between mother-to-daughter HSCT and father-to-child HSCT showed a lower relapse incidence in the former than in the latter ($P = .06$). Separate multivariable analyses of T cell-depleted HSCT and unmanipulated HSCT showed that maternal donor transplants were associated with lower relapse incidence in both T cell-depleted (HR, 2.13; 95% CI, 1.16 to 3.92; $P = .018$) and unmanipulated (mostly in vivo T cell-depleted with ATG; HR, 4.15; 95% CI, 0.94 to 18.35; $P = .06$) HSCT and better GRFS in T cell-depleted HSCT (HR, 1.67; 95% CI, 1.02 to 2.73; $P = .04$) (Supplementary Tables S2 to S5).

This study was designed to assess the potential role of the different donor-recipient kinships. As expected, patients who received transplants from maternal donors were younger than recipients of transplant from all other family members. Nonetheless, multivariable analyses showed no impact of age on the improved transplantation outcomes observed in the recipients of maternal donor transplants. In any event, we deemed it appropriate to perform the analysis in patients with comparable median age. To perform such an analysis, we used the 75th age percentile (ie, 25 years) of recipients of maternal donor transplants to set the upper age limit of patients to be evaluated. The median age was 13.1 years in the maternal donor transplant recipient and 16.9 in the recipients of transplants from all other family donors (see Supplementary Table S6 for demographic data). Univariable and multivariable analyses confirmed that transplantation from maternal donors was associated with significantly better PFS and GRFS and lower relapse incidence (Supplementary Figure S1 and Table S7).

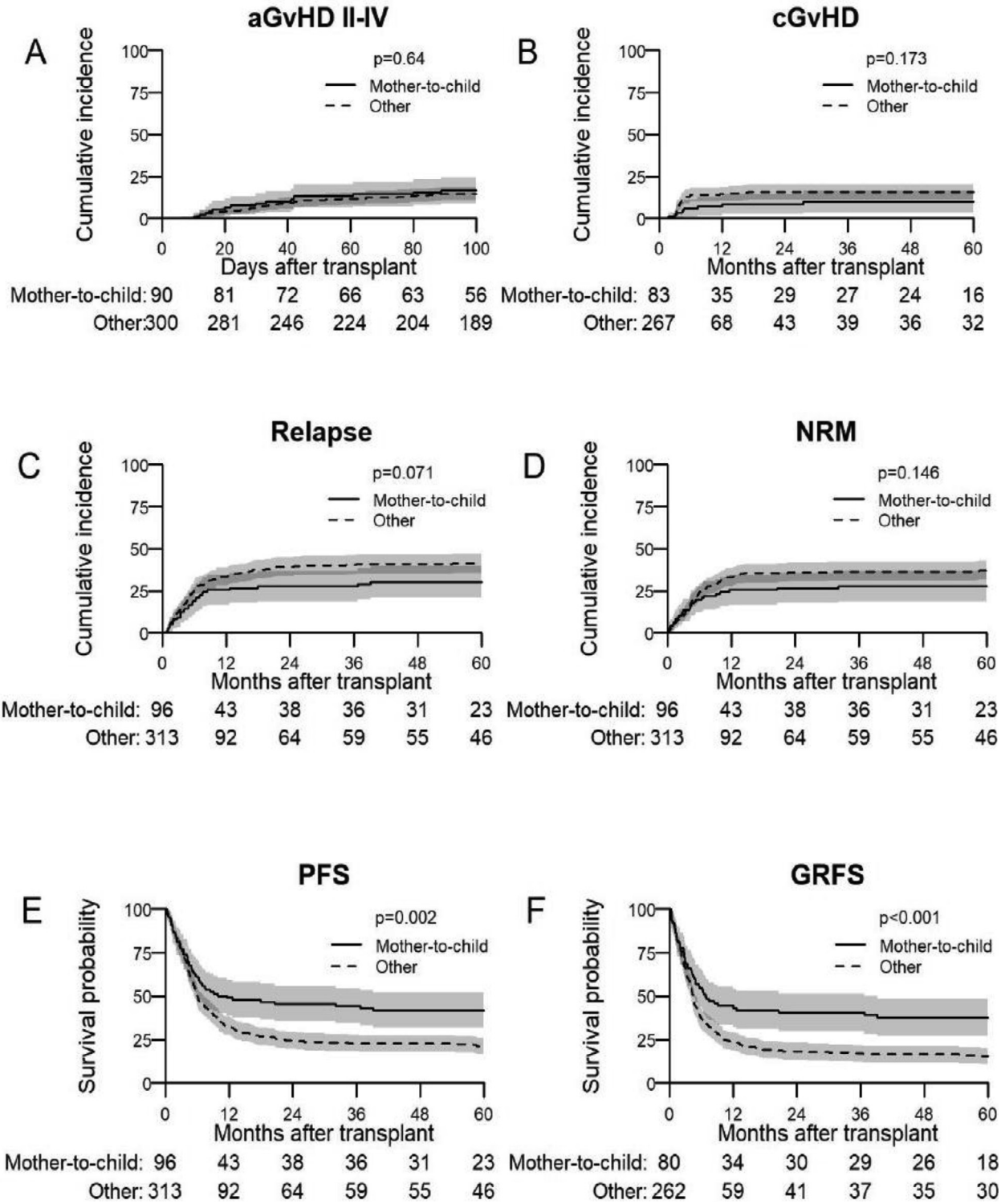

Figure 1. Outcomes after haploidentical HSCT from maternal donors versus all other family members. Unadjusted cumulative incidence of aGVHD (A), cGVHD (B), relapse (C), and NRM (D) and Kaplan-Meier estimates of PFS (E) and GRFS (F) for the entire patient cohort (ie, ex vivo T cell-depleted transplant as well as unmanipulated transplant recipients). The shaded areas indicate 95% CIs.

DISCUSSION

The present investigation of HLA haploidentical HSCT performed in 102 pediatric and 307 adult patients with acute leukemia shows that transplantation from a maternal donor is an independent factor predicting lower relapse rates and better GRFS compared with transplantation from any other family member donor. We intentionally included all patients regardless of age (up to age 70 years for recipients of transplants from other family donors) to challenge the hypothesis of the advantage of the mother donor effect. In fact, our multivariable analyses show the advantage of maternal donors regardless of age (Table 3). Stern et al. [8] and Kruchen et al. [9]

Table 2
Unadjusted 5-Year Kaplan-Meier Estimates of PFS and GRFS and 5-Year Cumulative Incidences of Relapse and NRM, Stratified by Risk Factors

Variable		PFS, % (95% CI)	*P*	Relapse, % (95% CI)	*P*	NRM, % (95% CI)	*P*	GRFS, % (95% CI)	*P*
Overall		26 (22-31)		39 (34-44)		35% (30-40)		21 (16-25)	
Donor	Mother	42 (32-52)	.002	30 (21-40)	.071	28 (19-37)	.15	38 (27-48)	<.001
	Other	21 (16-26)		41 (36-47)		37 (32-43)		15 (11-20)	
Age	<18 yr	40 (31-50)	.001	42 (32-52)	.5	18 (10-25)	<.001	36 (26-45)	<.001
	≥18 yr	21 (16-26)		38 (32-43)		41 (36-47)		15 (10-20)	
Status	CR	40 (33-47)	<.001	27 (21-34)	<.001	32 (26-39)	.07	35 (28-42)	<.001
	No CR	9 (5-13)		52 (45-59)		39 (32-46)		5 (1-8)	
KPS	<90	15 (7-24)	<.001	46 (34-57)	.1	39 (28-51)	.2	4 (0-9)	<.001
	90-100	29 (24-34)		37 (32-43)		33 (28-39)		24 (19-30)	
Ex vivo TCD	No	17 (9-24)	.001	48 (38-57)	.015	36 (27-45)	.6	4 (0-9)	<.001
	Yes	30 (25-36)		34 (29-40)		35 (30-41)		28 (22-34)	

P values are based on log-rank tests for PFS and GRFS and on Gray's test for relapse and NRM, comparing the curves of the different groups over the entire follow-up period.

demonstrated that maternal donors afford a clinical advantage in T cell-depleted haploidentical HSCT. Together, these studies and the present EBMT registry-based multicenter study demonstrate that use of a maternal donor is associated with improved outcomes of T cell-depleted haploidentical HSCT [10]. Our study also demonstrates a clinical advantage afforded by maternal donors in unmanipulated (mostly in vivo T cell-depleted with ATG) transplants (in which grafts were obtained from leukapheresis products), owing to a lower rate of leukemia relapse without an increased incidence of GVHD. A recent AIEOP-GITMO (Associazione Italiana Ematologia ed Oncologia Pediatrica and Gruppo Italiano Trapianto di Midollo Osseo) retrospective multicenter study in pediatric patients also demonstrated that transplantation from maternal donors was associated with a significantly reduced risk of relapse and better PFS in unmanipulated haploidentical HSCT in which post-transplantation cyclophosphamide was used as GVHD prophylaxis [11]. Other studies have shown that HSCT from maternal donors was associated with worse outcomes, due to either an increased incidence of aGVHD and NRM [12] or and increased incidence of relapse [13]. Such discrepancies may be related to differences in transplantation protocols and/or GVHD prophylaxis. For example, in the study by Wang et al. [12], the grafts were obtained by combining unmanipulated bone marrow and unmanipulated leukapheresis products. It may be speculated that sensitization of the maternal immune system to paternal alloantigens during pregnancy resulted in a higher incidence of aGVHD presumably because of the large number of T cells present in these combined grafts.

In conclusion, our data show that mothers should be preferred when selecting an HLA- haploidentical family donor for T cell-depleted HSCT. The improved survival in recipients of

Table 3
Multivariable Analyses of PFS, Relapse, NRM, and GRFS for the entire cohort by Cox Cause-Specific Hazards Models

Variable		**PFS**		**Relapse**		**NRM**		**GRFS**	
		HR (95% CI)	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Donor	Mother								
	Other	1.63 (1.1-2.41)	.015	2.16 (1.23-3.77)	.007	1.14 (0.65-2.01)	.6	1.57 (1.04-2.37)	.033
Ex vivo TCD	Yes								
	No	0.9 (0.66-1.23)	.5	0.99 (0.63-1.55)	>.99	0.79 (0.51-1.24)	.3	1.44 (1.03-2.01)	.034
In vivo TCD	Yes								
	No	0.98 (0.65-1.48)	.9	0.69 (0.37-1.28)	.2	1.37 (0.79-2.39)	.3	1.43 (0.9-2.27)	.13
Sex	Male								
	Female	1.15 (0.88-1.52)	.3	0.99 (0.67-1.45)	>.99	1.37 (0.92-2.04)	.12	0.93 (0.71-1.23)	.6
KPS	90-100								
	<90	1.36 (0.97-1.91)	.07	1.26 (0.8-1.99)	.3	1.42 (0.86-2.35)	.16	1.5 (1.05-2.15)	.026
Age (by decade)		1.01 (0.91-1.11)	.9	0.92 (0.8-1.05)	.2	1.13 (0.98-1.3)	.09	1 (0.9-1.11)	>.99
Leukemia type	AML								
	ALL	1.45 (1.07-1.98)	.016	1.79 (1.18-2.71)	.006	1.14 (0.72-1.81)	.6	1.52 (1.1-2.11)	.011
Graft source	BM								
	PBSCs	1.46 (0.76-2.83)	.3	2.2 (0.78-6.18)	.14	0.98 (0.41-2.31)	>.99	1.32 (0.66-2.62)	.4
Status	CR								
	No CR	2.9 (2.13-3.94)	<.001	4.04 (2.61-6.26)	<.001	2 (1.29-3.09)	.002	2.96 (2.14-4.1)	<.001
Patient CMV serostatus	Negative								
	Positive	1.65 (1.11-2.47)	.014	1.35 (0.82-2.24)	.2	2.17 (1.09-4.3)	.026	1.14 (0.75-1.72)	.5
Time from diagnosis to HSCT		0.99 (0.98-1)	.008	0.98 (0.97-0.99)	.003	1 (0.98-1.01)	.5	0.99 (0.98-0.99)	.002

maternal donor grafts derives mainly from a lower incidence of relapse without an increased incidence of aGVHD. The obvious limitation of this approach is the availability of a maternal donor; consequently, our results are particularly relevant for children, adolescents, and younger adults and not for older patients. Regarding unmanipulated HSCT, the conflicting results between our present data and the data of Berger et al. [11] and the data reported by Wang et al. [12] and Mariotti et al. [13] preclude recommending mothers as the preferred donors in this setting.

The better outcomes in mother-to-child transplantation may be the result of exposure of the mother's immune system to fetal antigens during pregnancy. Apparently, exposure of the maternal immune system to paternal alloantigens during pregnancy results in a unique form of immunologic memory whereby the mother's immune system exerts an alloreaction that results in a graft-versus-leukemia effect without an increased risk of GVHD. Further clinical and preclinical studies will unveil the mechanisms underlying mother-to-child immune interaction during pregnancy and its consequences in haploidentical HSCT for acute leukemia.

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SUPPLEMENTARY MATERIALS

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