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Can a Female Donor for a Male Recipient Decrease the Relapse Rate for Patients with Acute Myeloid Leukemia Treated with Allogeneic Hematopoietic Stem Cell Transplantation?

Piyanuch Kongtim, Antonio Di Stasi, Gabriela Rondon, Julianne Chen, Kehinde Adekola, Uday Popat, Betul Oran, Partow Kebriaei, Borje S. Andersson, Richard E. Champlin, Stefan O. Ciurea*

Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, Texas

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A B S T R A C T

The mismatched minor histocompatibility antigens present on Y chromosome (H-Y) in male recipients receiving stem cells from female donors may contribute to the graft-versus-leukemia effect and results in a reduced relapse rate, especially in patients with high-risk disease. We retrospectively compared the outcomes of male patients with acute myeloid leukemia who received an allogeneic hematopoietic stem cell transplant (HSCT) from female donors (F-M) (174 patients) versus other gender combinations (667 patients). Median age was 50 years (range, 18 to 74 years). For the whole group, the 1-year cumulative incidence of relapse was significantly lower in F-M group (34.1% versus 41.3%, $P = .044$), whereas nonrelapse mortality (NRM) was higher (23.2% versus 15.7%, $P = .004$). For patients younger than 50 years beyond first complete remission, the F-M group was associated with lower relapse rate (42.5% versus 55.2%, $P = .045$) whereas NRM was not significantly different (35.8% versus 25.5%, $P = .141$). Although survival was not significantly improved, transplantation from a female donor for male recipient was associated with a lower relapse rate. When relapse is the most common concern for treatment failure, especially for younger patients, a female donor for a male recipient might be beneficial to decrease relapse rate after transplantation. Future studies are needed to explore how the H-Y mismatch may improve survival after transplantation.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) represents a potentially curative therapy for patients with acute myeloid leukemia (AML) and other hematologic malignancies. The efficacy of transplantation against leukemic cells is the result of both conditioning chemotherapy and graft-versus-leukemia (GVL) effect, which is induced primarily by the minor histocompatibility antigens (miHA) present on the surface of leukemic cells [1,2]. Unfortunately, as some of these antigens are also expressed on the recipient's nonhematopoietic cells, alloreactivity against the recipient's tissues can lead to a potential fatal complication, graft-versus-host disease (GVHD). One of the miHA associated with GVL and GVHD is a group of Y chromosome–encoded proteins (H-Y) in male recipients, which may be recognized by T lymphocytes from female donors in the setting of a gender-mismatched transplantation. The stronger alloreactivity effect of the donor-recipient gender-mismatched HSCT was first described in the patients with aplastic anemia. Storb et al. reported the higher transplantation-related mortality and incidence of GVHD in aplastic anemia patients who received a gender-mismatched transplant, compared with gender-matched transplant recipients [3]. Later, several studies demonstrated that HSCT from female donors to male recipients (F-M), compared with all other donor-recipient gender combinations, was associated with a lower relapse rate in patients with hematologic malignancies [4-6]. However, whether or not there is an advantage of a stronger GVL effect in gender-mismatched transplantation, in particular using female donors for male recipients, remains unclear because of conflicting reports published to date [4-7]. Moreover, no data exist for AML patients. Younger patients may have lower treatment-related mortality and be able to better tolerate GVHD; thus, we hypothesized that such patients might

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* Correspondence and reprint requests: Stefan O. Ciurea, MD, The University of Texas MD Anderson Cancer Centre, 1515 Holcombe Blvd., Unit 423, Houston, TX, 77030.
E-mail address: sciurea@mdanderson.org (S.O. Ciurea).

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benefit from a stronger antitumor effect generated by using a female donor instead of the traditional male donor, when this option is available. We retrospectively analyzed the impact of donor-recipient gender mismatch on transplantation outcomes in a uniform large cohort of AML patients treated with busulfan-based conditioning and a matched donor at our institution.

PATIENTS AND METHODS

We analyzed transplantation outcomes of all 841 patients, 18 years or older (456 male, 385 female) with a diagnosis of AML who received their first transplant from an HLA-matched related (MRD) or 8/8 matched unrelated donor (MUD) at The University of Texas MD Anderson Cancer Center between January 1991 and June 2012. Clinical data were gathered at the time of transplantation. The median interval from diagnosis to transplantation was 8 months (range, 1 to 332 months); 453 (53.9%) and 388 patients (46.1%) received transplants from MRD and MUD, respectively.

All patients received a uniform conditioning regimen with fludarabine and busulfan, as previously reported by our group [8,9]. The great majority of patients received myeloablative conditioning (MAC) (93.7%), whereas 53 patients (6.3%) received a reduced-intensity conditioning regimen (RIC) with lower busulfan doses (area under the curve of 4000/day or less). Most frequent GVHD prophylaxis regimen was combined tacrolimus and methotrexate (n = 774, 92%). Patients were categorized into 2 groups according to donor-recipient gender combinations: female donor to male recipient (F-M) (n = 174) and other gender combinations (OGC) (n = 667).

The primary endpoints were progression-free survival (PFS), overall survival (OS), cumulative incidence of relapse (CIR), nonrelapse mortality (NRM), and acute and chronic GVHD. All outcomes were measured from the time of stem cell infusion. The date of neutrophil engraftment was defined as the first day of granulocyte counts greater than $.5 \times 10^9$/L for 3 consecutive days, derived at least in part from donor cells. The date of platelet engraftment was defined as the first day of platelet counts greater than 20,000/L for 7 consecutive days independent of transfusions. PFS was defined as the time between HSCT and disease relapse or death from any cause; data for patients who were alive without relapse was censored at the date of last contact. OS was defined as the time between HSCT and death from any cause; surviving patients were censored at the date of last contact. Relapse was defined as hematologic recurrence of AML according to World Health Organization criteria [10]. NRM was defined as death related to HSCT during continuous remission. OS and PFS were calculated using the Kaplan-Meier method. Univariate comparisons of all endpoints were completed by the log-rank test. Cumulative incidence was used to estimate the endpoints of relapse, NRM, acute GVHD, and chronic GVHD. A Cox proportion hazards model [11] or the Fine and Gray method [12] for competing hazards were used for multivariate regression. Variables were included in the multivariate models if they were conceptually important or if they approached ($P < .10$) or attained statistical significance in the univariate regression. All factors were tested for the proportional hazards assumption. Analyses were performed using SPSS statistics program for Mac OS version 20.0.

The institutional review board of the MD Anderson Cancer Center approved the treatment protocols and this retrospective study. All patients provided written informed consent for transplantation according to the Declaration of Helsinki.

RESULTS

Patients' characteristics are listed in Table 1. The median age was 50 years (range, 18 to 74 years). All 841 patients had de novo AML, except for 146 (17.3%) who had secondary or therapy-related AML. Two hundred and ninety-eight patients (35.4%) had high-risk cytogenetics at diagnosis according to the Medical Research Council (MRC) cytogenetic classification [13] and 561 patients (66.7%) were in remission before transplantation. Cytogenetics and molecular data according to the European Leukemia Net (ELN) classification [14] could be evaluated in 621 patients (252 patients were in adverse ELN risk group). There were no significant differences in baseline characteristics between the F-M and OGC groups, except there were more patients with secondary AML in the F-M group (22.9% versus 16.4%; $P = .018$). Sixty-one patients (35.1%) in the F-M group and 237 patients (35.5%) in the OGC group had high-risk cytogenetic according to MRC classification ($P = .652$). Fifty-three patients (30.4%) in the F-M group and 227 patients (34%) in the OGC group underwent transplantation with active disease ($P = .479$). Eight hundred and eighteen patients (97.3%) engrafted the donor cells (96% in F-M group and 97.6% in OGC group, $P = .397$) with a median time to neutrophil and platelet engraftment of 12 days and 13 days, respectively. There was no significant difference in time to neutrophil and platelet engraftment between the F-M and OGC groups ($P = .57$). At the time of last follow-up, 387 (46%) patients were alive, with median follow-up duration of 35 months (range, 3 to 241 months). Transplantation outcomes are summarized in Table 2.

Relapse

The CIR at 1 year for the entire cohort was 39.9%. When compared with patients in the OGC group patients in F-M group had a lower relapse rate, with a CIR at 1 year of 34.1% versus 41.3% in OGC group ($P = .044$) (Supplemental Figure 1). This difference was related to a significantly lower relapse rate for patients beyond first complete remission (CR) before transplantation, with a 1-year CIR of 39.8% in the F-M group versus 52% in the OGC group ($P = .039$) (Supplemental Figure 2), whereas patients who underwent HSCT in first CR had similar CIR (27.7% in F-M group, 31.2% in OGC, $P = .419$) (Supplemental Figure 3). We then analyzed the CIR of a subgroup of the patients who were not in first CR and younger than 50 years to see whether using a female donor for a male recipient had a benefit in younger patients with high-risk disease. In this age group, we have also found a significantly lower CIR in the F-M group (42.5%) compared with the OGC group (55.2%) ($P = .045$) (Figure 1A). Outcomes of F-M compared with OGC group stratified by age, donor-recipient race matching, disease characteristics and status, conditioning regimens, stem cell sources, and HSCT types are summarized in Table 3. The benefit of using a female donor for a male recipient in lowering the rate of relapse was also seen in subgroup of patients who were younger than 50 years, not in remission before transplantation, received myeloablative conditioning, received peripheral blood stem cells, and from an MRD. Beside donor-recipient gender combinations, other factors associated with increased risk of relapse in univariate analyses were high-risk cytogenetics, adverse ELN risk, disease beyond first CR at transplantation, transplantation using RIC, and the presence of mixed donor-recipient chimerism early after transplantation, whereas having chronic GVHD was associated with a lower relapse rate (Table 4). All of these factors retained statistical significance in multivariate regression analysis (Table 5). In addition, using a female donor for a male recipient was an independent prognostic factor for lower relapse, with hazard ratio of .71 (95% confidence interval, .47 to .91; $P = .04$).

NRM

NRM at 1 year of the whole cohort was 17%. According to donor-recipient gender combinations, patients in F-M group had significantly higher NRM compared with those in the OGC group, with 1-year NRM of 23.2% versus 15.7%, respectively ($P = .004$) (Supplemental Figure 4). When compared with the OGC, F-M group had higher incidence of fatal acute GVHD (8.5% versus 2.3%, $P = .031$), chronic GVHD (7.1% versus 1.4%, $P = .027$), and death from infections (11.6% versus 2.4%, $P = .025$).

Again, the statistical significance was seen in subgroup patients who were not in first CR before HSCT (29.1% in F-M group versus 17.4% in OGC group, $P = .004$) (Supplemental

Table 1
Patient and Transplantation Characteristics

Characteristic	All Patients			First CR			Beyond First CR			Beyond First CR, < 50 Years		
	F-M (n = 174)	OGC (n = 667)	*P* Value	F-M (n = 89)	OGC (n = 334)	*P* Value	F-M (n = 81)	OGC (n = 323)	*P* Value	F-M (n = 46)	OGC (n = 182)	*P* Value
Age, median (IQR), yr	50 (18-74)	50 (19-72)	.68	53 (19-71)	51 (18-74)	.547	48 (19-79)	48 (18-70)	.329	35 (19-50)	36 (18-50)	.96
Age > 60 yr	33 (19)	111 (16.6)	.498	15 (16.9)	64 (19.2)	.76	18 (22.2)	43 (13.3)	.056	0	0	
Diagnosis			.002			.941			.004			.234
AML	134 (77)	561 (84.1)		74 (83.1)	282 (84.4)		59 (72.8)	271 (83.9)		40 (87)	169 (92.9)	
MDS/AML	29 (16.7)	96 (14.4)		14 (15.7)	49 (14.7)		14 (17.3)	45 (13.9)		5 (10.9)	12 (6.6)	
MPN/AML	11 (6.3)	10 (1.5)		1 (1.1)	3 (.9)		8 (9.9)	7 (2.2)		1 (2.2)	1 (.5)	
MRC cytogenetic risk			.652			.592			.822			.64
Good	8 (4.6)	43 (6.4)		1 (1.1)	11 (3.3)		6 (7.4)	31 (9.6)		3 (6.5)	22 (12.1)	
Intermediate	97 (55.7)	366 (54.9)		51 (57.3)	186 (55.7)		44 (54.3)	173 (53.6)		28 (60.9)	94 (51.6)	
High	61 (35.1)	237 (35.5)		35 (39.3)	133 (39.8)		25 (30.9)	102 (31.6)		13 (28.3)	53 (29.1)	
ELN classification			.90			.716			.927			.818
Favorable	14 (10.7)	65 (13.3)		4 (5.5)	24 (8.9)		9 (16.4)	40 (19)		6 (20)	26 (23.9)	
Intermediate-I	23 (17.6)	83 (16.9)		17 (23.3)	55 (20.3)		6 (10.9)	25 (11.8)		5 (16.7)	12 (11)	
Intermediate-II	39 (29.8)	145 (29.6)		19 (26)	80 (29.5)		19 (34.5)	63 (29.9)		8 (26.7)	27 (24.8)	
Adverse	55 (42)	197 (40.2)		33 (45.2)	112 (41.3)		21 (38.2)	83 (39.3)		11 (36.7)	44 (40.4)	
Treatment before HSCT												
>1 Cycle of chemotherapy	173 (99.4)	660 (99)	.776	18 (20.2)	109 (25.8)	.789	80 (98.8)	318 (97.8)	.495	45 (97.8)	180 (98.9)	.413
Prior AlloHSCT	6 (3.4)	15 (2.4)	.619	1 (1.1)	3 (.9)	1.0	5 (6.2)	13 (4.0)	1.0	3 (6.5)	6 (3.3)	.39
Prior ASCT	2 (1.1)	6 (.7)	.428	1 (1.1)	2 (.6)	.509	1 (1.2)	3 (0.0)	.376	0	0	
Response before HSCT			.479			1.0			.322			.075
CR1	89 (51.1)	334 (50)		89 (100)	334 (100)		0	0		0	0	
CR2	28 (16)	101 (15.1)		0	0		24 (29.6)	101 (31.3)		19 (41.3)	61 (33.5)	
CR3+	4 (2.3)	5 (.8)		0	0		3 (4.9)	5 (1.5)		4 (8.7)	4 (2.2)	
Active disease	53 (30.4)	227 (34)		0	0		53 (31.2)	207 (33.1)		23 (50)	117 (64.3)	
RIC	10 (5.7)	43 (6.4)	.862	3 (3.4)	16 (4.8)	.775	7 (8.6)	25 (7.7)	.818	0	8 (4.4)	.364
Stem cell source			.055			.007			.442			.866
Peripheral blood	130 (74.7)	424 (63.6)		72 (80.9)	219 (65.6)		54 (66.7)	199 (61.6)		28 (60.9)	114 (62.6)	
Marrow	44 (25.3)	243 (36.4)		17 (19.1)	115 (34.4)		27 (33.3)	124 (38.4)		18 (39.1)	68 (37.4)	
Donor			.101			.001			.213			.74
MRD	114 (65.5)	339 (50.8)		62 (69.7)	168 (50.3)		49 (60.5)	168 (52)		26 (56.5)	108 (59.3)	
MUD	60 (34.5)	328 (49.2)		27 (30.3)	166 (49.7)		32 (39.5)	155 (48)		20 (43.5)	74 (40.7)	
Engraftment	167 (96)	651 (97.6)	.397	85 (95.5)	326 (97.6)	.166	79 (97.5)	315 (97.5)	.738	46 (100)	179 (98.4)	1.0
Median time to ANC/platelet engraftment, d	12/13	12/13	1.0	12/13	12/14	.94	12/13	12/13	1.0	12/14	12/14	1.0
Day 30 donor chimerism			.957			.370			.713			.706
Donor	92 (55.1)	361 (55.7)		42 (48.8)	166 (50.5)		49 (62.8)	191 (61.8)		33 (76.7)	113 (66.5)	
Mixed	72 (43.1)	208 (41.1)		44 (51.2)	155 (47.1)		26 (33.3)	107 (34.6)		9 (20.9)	48 (28.2)	
Autologous	0	1 (.2)		0	0		0	1 (.3)		0	1 (.6)	
Final response			.598			.881			.215			.211
CCR/CR	155 (92.3)	612 (92.9)		84 (97.7)	315 (95.7)		67 (85.9)	288 (90)		41 (91.1)	166 (91.7)	
NR	9 (5.4)	38 (5.8)		1 (1.2)	9 (2.7)		8 (10.3)	28 (8.8)		2 (4.4)	13 (7.2)	
ED	4 (2.4)	9 (1.4)		1 (1.2)	5 (1.5)		3 (3.8)	4 (1.2)		2 (4.4)	2 (1.1)	

IQR indicates interquartile range; MDS/AML, acute myeloid leukemia arising from myelodysplastic syndrome; MPN/AML, acute myeloid leukemia arising from myeloproliferative neoplasm; MRC, The Medical Research Council; ELN, European Leukemia Net; AlloHSCT, allogeneic hematopoietic stem cell transplantation, ASCT, autologous stem cell transplantation; MUD, matched unrelated donor; ANC, absolute neutrophil count; CCR, complete cytogenetic remission; NR, not in remission; ED, early death.
Data presented are n (%) unless otherwise indicated.

Table 2
Transplantation Outcomes of F-M and OGC Group Stratified by Remission Status before Transplantation

Outcomes	All Patients			First CR			Beyond First CR			Beyond First CR, < 50 Years		
	F-M (n = 174)	OGC (n = 667)	*P* Value	F-M (n = 89)	OGC (n = 334)	*P* Value	F-M (n = 81)	OGC (n = 323)	*P* Value	F-M (n = 46)	OGC (n = 182)	*P* Value
1-Year CIR	34.1	41.3	.044	27.7	31.2	.419	39.8	52	.039	42.5	55.2	.045
1-Year NRM	23.2	15.7	.004	17.2	13.5	.258	29.1	17.4	.004	35.8	25.5	.141
Acute GVHD												
All grades	51.1	50.4	.691	48.3	48.8	.479	54.3	52.3	.612	52.2	46.7	.701
Grade 2/4	28.2	28.3	1.0	16.9	27.5	.104	39.5	30.2	.186	32.6	25.5	.488
Grade 3/4	10.3	5.8	.042	4.5	3.9	.764	16	8	.036	17.4	7.7	.055
Chronic GVHD												
All grade	44.3	37.8	.132	50.6	41	.418	38.3	34.7	.284	41.3	41.2	.266
Extensive	34.5	26.5	.047	37.1	27.5	.09	33.3	25.4	.162	39.1	31.1	.38
3-Year OS	43.4	44	.449	55.3	53.7	.706	32.8	34	.601	32.4	40.1	.21
3-Year PFS	40.3	38.3	.943	52.4	47.1	.984	29.7	29.2	.737	32.8	32.9	.956

Data presented are %, unless otherwise indicated.

Figure 5), whereas the patients who underwent transplantation in first CR had comparable NRM (17.2% in F-M group versus 13.5% in OGC group, $P = .258$) (Supplemental Figure 6). However, for patients younger than 50 years beyond first CR, the NRM was not significantly different (35.8% in F-M group versus 25.5% in OGC group, $P = .141$) (Figure 1B). These results suggest that this subgroup of patients might benefit from a gender-mismatched transplantation (Table 2). Beside remission status, NRM of F-M group was higher than in OGC group in subgroups of the patients older than 50 years, having secondary AML, with active disease before HSCT, receiving peripheral blood stem cells, and with MRD. Interestingly, using gender- and race-mismatched donor together did not influence the incidence of NRM (Table 3). Factors associated with higher NRM in univariate analyses were age, disease beyond first CR before transplantation, and the development of acute GVHD (Table 4). All of these factors, as well as transplantation in male patients using stem cells from female donors, retained their prognostic significance in multivariate analysis (Table 5).

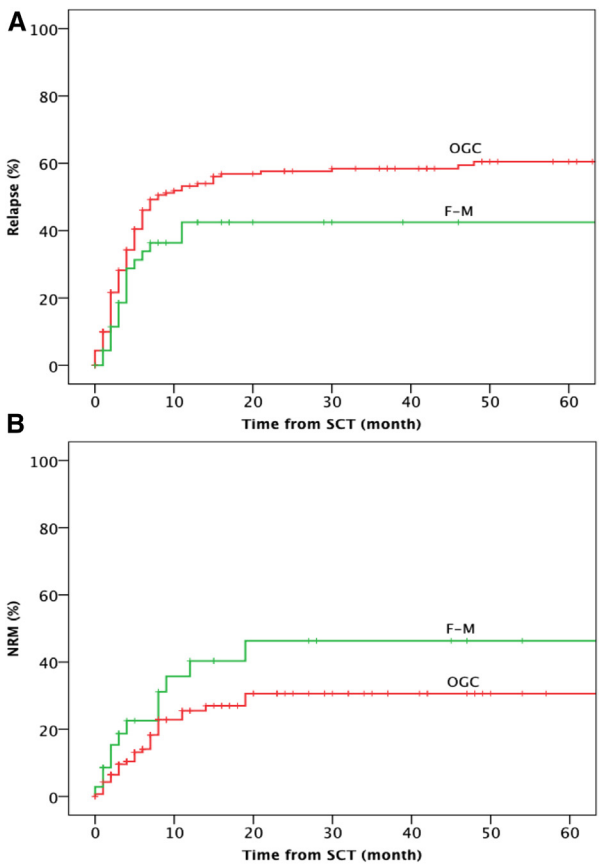

Figure 1. (A) Shows CIR and (B) shows NRM of patients beyond first CR younger than 50 years.

GVHD

Although the cumulative incidence of all grades acute GVHD was comparable between the F-M (51.1%) and OGC groups (50.4%), ($P = .691$), the incidence of grade 3 and 4 acute GVHD was significantly higher in the F-M group (10.3% versus 5.8%, $P = .042$). A higher incidence of severe acute GVHD (grade 3 and 4) was also seen in patients beyond first CR before transplantation (16% in the F-M group versus 8% in the OCG group, $P = .036$). Moreover, in patients beyond first CR who were younger than 50 years, the cumulative incidence of grades 3 and 4 acute GVHD had a trend to be higher in F-M group (17.4% in the F-M group versus 7.7% in the OGC group, $P = .055$). A similar incidence of chronic GVHD all grades was seen in both groups (44.3% in F-M group, 37.8% in OGC group, $P = .132$). However, a higher incidence of chronic extensive GVHD was found in the F-M group than those in the OGC group (34.5% versus 26.5%, $P = .047$).

Survival

The benefit of the GVL effect resulted in a lower relapse rate in the F-M group. However, because of higher NRM related primarily to higher incidences of acute GVHD grades 3 and 4 and chronic extensive GVHD, this benefit did not translate into superior survival compared with OGC group. Three-year PFS of the entire cohort was 38.7%. There was no significant difference in PFS of F-M and OCG group (3-year PFS 40.3% in the F-M group versus 38.3% in the OGC group; $P = .943$) (Supplemental Figure 7).

Three-year OS of the whole cohort was 43.9%. Again, there was no significant difference in OS of the F-M and OGC groups. Three-year OS was 43.4% in the F-M group versus 44% in the OGC group ($P = .449$) (Table 2) (Supplemental Figure 8). The similar PFS and OS of all donor-recipient gender combinations were also seen in subgroup of the patients in first CR or beyond first CR. The PFS and OS were also similar even for patients beyond first CR younger than 50 years who had lower CIR and yet comparable NRM, which means that the protection from relapse of F-M transplantation was not strong enough to balance the risk of

Table 3
Transplantation Outcomes of F-M and OGC Group Stratified by Patient and Transplantation Characteristics

Factor	3-Year PFS			3-Year OS			1-Year CIR			1-Year NRM		
	F-M	OGC	*P* Value	F-M	OGC	*P* Value	F-M	OGC	*P* Value	F-M	OGC	*P* Value
Age												
< 50 Yr	42.7	40.9	.793	43.7	48.8	.208	34.1	41.7	.036	20.4	11.6	.243
≥ 50 Yr	37.7	35.4	.693	43.4	38.6	.825	33.7	40.9	.215	26.1	17.7	.003
Race mismatched												
Yes	47.6	46.5	.880	40	52.7	.904	30.6	34.4	.713	25	7.1	.758
No	44.8	39.3	.657	45.5	45.2	.603	34.2	42	.118	21.4	16.2	.066
Secondary AML												
Yes	31	29.2	.873	37.1	30.6	.825	45.2	47.5	.808	33.4	23.1	.868
No	41.8	40.1	.972	43.8	46.9	.208	32.3	40.2	.084	19.9	14	.005
High-risk cytogenetics												
Yes	37	33.2	.936	40.8	37.7	.866	46.8	48.3	.626	14.9	17.5	.326
No	37.5	44.6	.665	50	48.5	.797	12.5	24.6	.970	27.1	22.6	.505
ELN classification												
Favorable	49.8	42	.681	55.6	52.3	.757	23.2	26.8	0.549	25.3	27.3	.435
Intermediate-I	43.4	46.3	.557	49.5	51.8	.625	26.9	24.2	0.896	29.0	27.1	.487
Intermediate-II	45.3	47.7	.870	47.2	50.3	.451	30.2	26.5	0.384	24.4	22.4	.797
Adverse	27.3	29.4	.838	31.3	35.2	.365	45.2	41.3	0.496	26.3	25.1	.965
Active disease												
Yes	29.8	19.9	.623	21.1	24.6	.575	50.3	60.7	.029	37.9	18.6	.002
No	52.5	47.5	.885	55.9	53.8	.786	25.7	32.5	.271	16.5	14	.201
Conditioning regimens												
RIC	10	21.8	.392	20	22.8	.495	60	58	.816	34.4	22.3	.376
MAC	42.2	39.4	.823	44.9	45.5	.519	32.3	40.2	.045	23.7	16.6	.006
SC sources												
Peripheral blood	43.4	37.2	.731	42.4	43.4	.258	32.8	40.9	.028	25.1	14.2	.003
Marrow	31.8	40.1	.650	46.5	44.8	.709	37.6	41.8	.938	21	17.6	.421
HSCT types												
MRD	45.5	36.7	.230	46.2	43	.991	37.6	42.8	.005	22.1	14.3	.017
MUD	30.4	40.2	.128	38.5	45.4	.172	46.8	39.5	.486	25.3	16.5	.125

MAC indicates myeloablative conditioning; SC, stem cell.
Data presented are %, unless otherwise indicated.

GVHD and NRM and influence the survival. A relatively low number of patients could have contributed to the failure to identify a significant difference in survival for this group.

Other factors associated with poor PFS in univariate analyses were adverse ELN risk, disease beyond first CR before transplantation, use of a RIC regimen, and mixed donor-recipient chimerism early after transplantation, whereas chronic GVHD was associated with better PFS and OS (Table 4). In multivariate analyses for PFS and OS, independent prognostic factors for better outcomes were transplantation in first CR and the development of cGVHD, whereas adverse ELN risk and the use of RIC had a negative impact (Table 5).

DISCUSSION

In this study, we analyzed the impact of female donors to male recipients in a large cohort of AML patients treated with the same conditioning regimen at a single institution. To our knowledge, this is the first study conducted in a homogeneous group of patients with AML treated with the same conditioning regimen to determine the impact of donor-recipient gender matching on outcomes of hematopoietic stem cell transplantation. Our results clearly demonstrated that male patients with AML had a lower relapse rate when they received a gender-mismatched transplant. These beneficial effects were, in general, offset by a higher treatment-related mortality, related by a higher incidence of GVHD and overall similar survival outcomes. These findings

Table 4
Univariate Analyses for PFS, OS, RI, and NRM

Factors	PFS		OS		RI		NRM	
	HR	*P* Value	HR	*P* Value	HR	*P* Value	HR	*P* Value
Age	1.084	.72	1.144	.004	1.03	.059	1.215	.014
F-M	1.096	.945	1.044	.467	.872	.041	1.279	.005
Race mismatched	1.095	.155	1.095	.194	.803	.452	1.641	.33
Secondary AML	1.201	.08	1.18	.12	1.263	.093	1.231	.225
High-risk cytogenetics	1.124	.201	1.12	.243	1.405	.004	1.485	.195
Adverse ELN risk	1.669	<.001	1.756	<.001	1.342	.031	1.1	.842
Beyond first CR	1.717	<.001	1.7	<.001	1.348	<.001	1.194	.027
RIC	1.374	<.001	1.209	<.001	1.469	<.001	.741	.339
Marrow stem cells	1.05	.851	1.023	.656	1.009	.855	.988	.884
MUD	1.011	.906	1.006	.895	1.029	.602	1.028	.727
Mixed chimerism	1.792	<.001	1.034	.496	1.105	.004	1.198	.309
Acute GVHD	1.129	.501	1.097	.327	.836	.097	1.719	.001
Chronic GVHD	.333	<.001	.475	<.001	.303	<.001	1.15	.451

RI indicates relapse incidence; HR, hazard ratio.

Table 5
Multivariate Analyses for PFS, OS, RI, and NRM

Factor	HR	95% CI	*P* Value
Prognostic factors for PFS			
Beyond first CR	.45	.38-.69	<.001
RIC	1.97	1.31-2.84	.001
Mixed chimerism	1.13	.94-1.62	.135
Chronic GVHD	.64	.41-.84	<.001
Adverse ELN risk	1.71	1.37-2.13	<.001
Prognostic factors for OS			
Age	1.01	.91-1.22	.331
Beyond first CR	.57	.46-.81	<.001
RIC	2.14	1.39-2.99	<.001
Chronic GVHD	.55	.38-.79	.002
Adverse ELN risk	1.82	1.32-2.43	<.001
Prognostic factors for CIR			
F-M	.71	.47-.91	.04
High-risk cytogenetics	1.40	1.08-1.81	.01
RIC	1.92	1.25-2.95	.003
Beyond first CR	2.48	1.35-2.68	<.001
Mixed chimerism	1.17	1.03-1.33	.015
Chronic GVHD	.52	.35-.77	.001
Adverse ELN risk	1.27	1.11-1.45	.045
Prognostic factors for NRM			
F-M	1.28	1.02-1.61	.031
Age	1.45	1.01-2.11	.048
Acute GVHD	1.65	1.18-2.30	<.001
Beyond first CR	1.24	1.05-1.46	.009

CI indicates confidence interval.

raise the question: is there a group of patients who will benefit from a female donor? Although younger male patients with advanced disease seem to benefit the most from transplantation with a female donor due to significantly lower relapse and comparable NRM, this did not translate into improved survival, either.

The association between gender-mismatched transplantation and risk of NRM has been reported in several other studies [4,7,15,16]. In a retrospective European Group for Blood and Marrow Transplantation analysis on patients with leukemia (including 1405 patients with AML), the authors showed that female donors to male recipients, compared with OGC, significantly influenced risk of NRM in both AML and acute lymphoid leukemia (ALL) [15]. Later, Randolph et al. retrospectively studied outcomes of 3238 patients with hematologic malignancies from the Fred Hutchinson Cancer Center. In this study, the female to male combination was associated with increased risk of death and higher incidence of extensive chronic GVHD [4]. Overall, we found that NRM was significantly higher in the F-M group compared with the OGC group, but only in patients beyond first CR, whereas NRM for patients who underwent transplantation in first CR was not different. This higher NRM in the F-M group was paralleled by higher incidences of grades 3 and 4 acute GVHD as well as chronic extensive GVHD. These findings suggests that mismatch in miHA located on the Y chromosome might play an important role in the pathogenesis of GVHD and results in increased NRM in F-M transplantation. However, in multivariate analysis, we found that both F-M transplantation and acute GVHD were independent prognostic factors for NRM, with hazard ratios of 1.28 and 1.65, respectively. These results illustrate that there is not a simple association between gender mismatch, GVHD, and NRM. Therefore, factors that influence NRM in F-M transplantation and the relationship with the development of GVHD remain to be clarified.

The miHA on the Y chromosome in male patients also influence immune-mediated antitumor effects when recognized by T cells from female donors. Our study results showed that transplantation with a female donor for male recipients was associated with a lower relapse rate when compared with OGC, which is consistent with the previous report in chronic myeloid leukemia (CML) patients by Gratwohl et al. In this study, the authors found a decreased risk of relapse in male patients who received grafts from female donors compared with female recipients from female donors [6].

Whether AML patients benefit from reduction of relapse rate in gender-mismatched transplantation, in particular F-M gender combination, was unclear. In 2004, Randolph et al. studied outcomes of 3238 patients who underwent allogeneic stem cell transplantation for various hematologic malignancies (including 1023 AML patients). This group found that male patients with female donors had a lower risk for relapse compared with all other donor-recipient gender categories. However, a statistically significant difference was seen only in patients with CML, whereas patients with AML and ALL had similar relapse rate in all donor-recipient gender combinations [4]. Here, we were able to show a lower relapse rate associated with a female donor for male recipients in a uniform cohort of AML patients. Furthermore, we found that F-M transplantation was an independent prognostic factor for lower relapse in multivariate analysis. These results indicate that the benefit of chromosome Y-dependent GVL effect might need more time than the increased NRM from acute GVHD. Overall, the benefit of lower relapse rate with a female donor for male recipient did not translate into survival advantage because of an increased risk of NRM. Consequently, we tried to identify a group of patients who might have a survival benefit from a stronger GVL effect using a female donor. Male patients younger than 50 years with high-risk disease (who underwent transplantation beyond first complete remission) had a 13% lower risk of relapse when a female donor was used. Survival of male recipients with a female donor in our study was at least as good as with a male donor. Nevertheless, our study results are different from the previous report by Stern et al., who compared transplantation outcomes of F-M and OGC in 53,988 patients with hematologic malignancies (including 3701 AML patients) from the European Group for Blood and Marrow Transplantation. They found that NRM in F-M HSCT was greater than protection from relapse, leading to a net negative effect on OS (43.2% in F-M versus 46.7% in OGC, $P < .001$). However, when the analyses were done for each type of leukemia separately, the significant difference was seen in CML (48% versus 55.4%, $P < .001$) and a trend was noted for patients with AML (44.4% versus 46.2%, $P = .07$), whereas OS of F-M and OGC were comparable in patients with ALL (40.9% versus 41.9%, $P = .54$) [16].

Our findings also raise other questions: with a different method of GVHD prevention, for example post-transplantation cyclophosphamide, which could result in better control of GVHD and a lower NRM, would a net favorable effect in survival be obtained for the F-M combination? Furthermore, whether a gender mismatch donor lymphocyte infusion is more effective to decrease relapse rate remains unclear.

In conclusion, our results indicate a strong GVL effect mediated by the minor H-Y antigens in patients with AML, which could be exploited in the future. Younger male patients with advanced disease could be considered for a female donor, as the relapse rate appears significantly better, although, at least for now, outcomes are not significantly

better. Such donor does not appear to be justified for patients in remission at transplantation. Future larger registry studies with focus on AML patients are needed to confirm these findings, as this could influence donor selection. Moreover, novel methods of GVHD prevention, such as post-transplantation cyclophosphamide, may decrease the incidence of acute and chronic GVHD and tilt the balance in favor of lower relapse rate with a net effect on improved survival for these patients.

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SUPPLEMENTARY DATA

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