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Donor and recipient sex in allogeneic stem cell transplantation: what really matters

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ABSTRACT

We investigated whether and how recipient-donor sex affects transplantation outcomes of 11,797 patients transplanted between 2008 and 2010. Thirty-seven percent were male recipients with male donors, 21% male recipients with female donors, 25% female recipients with male donors, and 17% female recipients with female donors. In multivariable analyses, male recipients had inferior overall survival and progression-free survival compared to females regardless of donor sex, with an 11% relative increase in the hazard of death (P<0.0001) and a 10% relative increase in the hazard of death or relapse (P<0.0001). The detrimental effect of male recipients varied by donor sex. For male recipients with male donors, there was a 12% relative increase in the subdistribution hazard of relapse compared with female recipients with male donors (P=0.0036) and male recipients with female donors (P=0.0037). For male recipients with female donors, there was a 19% relative increase in the subdistribution hazard of non-relapse mortality compared with male recipients with male donors (P<0.0001) and a 22% relative increase compared with female recipients with male donors (P=0.0003). In addition, male recipients with female donors showed a 21% relative increase in the subdistribution hazard of chronic graft-*versus*-host disease (P<0.0001) compared with female recipients with male donors. Donor sex had no effect on outcomes for female recipients. Transplantation of grafts from male and female donors was associated with inferior overall survival and progression-free survival in male recipients with differing patterns of failure. Recipient sex is an important prognostic factor independent of donor sex.

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Introduction

In patients undergoing allogeneic hematopoietic cell transplantation (HSCT), it has been previously reported that sex mismatch between donor and recipient affects HSCT outcome across diseases.[1-11] Most studies have reported that the combination of male recipient and female donor (F→M) is associated with a higher incidence of graft-*versus*-host disease (GvHD)[2,5,7,9] and non-relapse mortality (NRM),[1,3] as well as, in some studies, a lower relapse rate.[2,3] The increased GvHD rate in this setting is thought to be mediated *via* male recipient minor histocompatibility antigens (mHAs) targeted by female donor T cells,[10,11] and likely explains the increased NRM. At the same time, the theoretical increase in graft-*versus*-tumor (GvT) mediated by the same mHAs may explain the decreased risk of relapse. On balance, however, the increased toxicity of F→M transplants resulted in a decreased survival, suggesting that this combination was deleterious in patients undergoing

HSCT.[1-3] F→M is, therefore, included as a risk factor in the (modified) EBMT risk score,[12-16] and many transplant clinicians will use sex matching as a criterion in donor selection for patients undergoing HSCT. However, much less attention has been paid to recipient sex, although there have been a few reports that male recipients had a poor survival irrespective of donor sex.[2,3] Moreover, the exact sex-based determinants of HSCT outcome have not been rigorously examined in a modern transplantation cohort that is carefully stratified by disease risk. Recently, a study of disease risk conducted at a single institution found that the only significant risk factor for mortality related to sex was recipient sex, with a hazard ratio for mortality of approximately 0.9 for female compared to male recipients.[17] Given this, we undertook an analysis of donor/recipient sex in a large cohort of patients transplanted between 2008 and 2010 in the United States and reported to the Center for International Blood and Marrow Transplant Research (CIBMTR). The primary goal of this study was to examine the effect of recipient sex and donor-recipient sex combinations on overall and progression-free survival (OS and PFS) after HSCT. In addition, we sought to determine whether the effect of recipient and/or donor sex on OS and PFS were mediated mainly by acute or chronic GvHD, NRM, or relapse.

Methods

Study population

The Center for International Blood and Marrow Transplant Research (CIBMTR) comprises a voluntary network of more than 450 transplantation centers worldwide that contribute detailed data on consecutive allogeneic and autologous HSCT to a centralized Statistics Center.[18] Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected Health Information used in the performance of such research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the HIPAA Privacy Rule. The Institutional Review Board of the National Marrow Donor Program approved this study. The study cohort consisted of patients aged 18 years or over who underwent HSCT between 2008 and 2010, excluding autologous, syngeneic, and cord transplantations. Among the 14,126 potential patients, we further excluded 2329 patients (16%) with missing disease type or pre-transplant disease status, and transplantations for benign or rare disorders (including histiocytic disorders, large granular lymphocyte or natural killer cell leukemia). The remaining 11,797 patients are included in the current analysis.

Statistical analysis

Patients' baseline characteristics were reported descriptively. End points of interest were OS, PFS, relapse, NRM, as well as acute and chronic GvHD. OS was defined as the time from stem cell infusion to death from any cause. Patients who were alive were censored at the time last seen alive. PFS was defined as the time from stem cell infusion to disease relapse, progression or death from any cause, whichever occurred first. Patients who were alive without disease relapse or progression were censored at the time last seen alive and progression-free. OS and PFS were estimated using the Kaplan-Meier method and the log rank test stratified by conditioning intensity was used for comparisons of Kaplan-Meier curves. Cumulative incidence curves for non-relapse death, relapse and chronic GvHD were constructed in the competing risks framework considering relapse, NRM and death or relapse without developing chronic GvHD, respectively, as competing events. All time to events were measured from the date of stem cell infusion. The difference between cumulative incidence curves in the presence of a competing risk was tested using the Gray method.[19] Multivariable regression analysis was performed using the Cox model for OS, PFS and Fine and Gray model for relapse, NRM, and chronic GvHD.[20,21] Models were stratified by conditioning intensity as this variable did not meet the proportional hazards assumption. Potential prognostic factors considered in the analyses included recipient and donor sex, disease risk index (DRI),[17,18] age, conditioning intensity, cytomegalovirus (CMV) serostatus of recipient and donor, graft source, donor HLA type,[22] co-morbidity index (HCT-CI),[23] and Karnofsky performance status at HSCT. Prior to modeling, the proportional hazards assumption and significance of interaction terms were examined. Acute GvHD was analyzed as a binary outcome using a landmark analysis at day 100 of HSCT, and multivariable analysis for acute GvHD was performed using logistic regression analysis. The threshold for statistical significance was set at 0.01 to account for multiple testing. All tests were two-sided and all analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA), and R v.3.2.2 (the CRAN project; *www.cran.r-project.org*).

Results

Patients' characteristics

The baseline characteristics of the 11,797 patients are shown in Table 1. The median age of the entire cohort was 52 years (range 18-80). The cohort included a broad representation of diseases, disease risk, donor types, and graft sources. Forty-one percent of patients received grafts from matched sibling donor; 54% were conditioned with a myeloablative regimen. Among the 11,797 patient/donor pairs, 37% were male recipients with male donors (M→M), 21% male recipients with female donors (F→M), 25% female recipients with male donors (M→F), and 17% female recipients with female donors (F→F). Overall, 54% of pairs were sex matched: 42% among female recipients and 64% among male recipients (P<0.0001). The median follow up among survivors was 48 months (range 2-76).

Overall and progression-free survival

Overall, male recipients had worse OS and PFS than females, regardless of donor sex (Figures 1A and B and *Online Supplementary Table S1*). The 4-year OS was 41% in male recipients (41% for M→M and 40% for F→M) and 45% in female patients (45% for M→F and 44% for F→F) (P=0.001); the corresponding 4-year PFS was 33% in male recipients (33% for M→M and 32% for F→M) and 36% in female patients (37% for M→F and 35% for F→F) (P=0.0005). The result was consistent in multivariable analysis; hazard ratio (HR) of male compared to female recipients was 1.11 (95%CI: 1.05-1.16) for OS (P<0.0001) and 1.10 (95%CI: 1.05-1.15) for PFS (P<0.0001) (Table 2A). When all possible recipient and donor sex combinations were considered in the multivariable model, the F→M group showed an inferior OS (HR 1.14, P=0.0004) and PFS (HR 1.1 P=0.0044) compared with the M→F group (reference group). Worse survival outcome was also seen in the M→M group (HR 1.1, P=0.0032 for OS; HR 1.11, P=0.0004 for PFS), but not in the F→F group (HR 1.02 for both OS and PFS; P=0.64 and P=0.58, respectively) (Table 2B). When the F→M group was compared with the

Table 1. Baseline characteristics.

	Female recipients		Male recipients		
	F→F N (%)	M→F N (%)	M→M N (%)	F→M N (%)	All N (%)
Number of patients	2061 (17)	2899 (25)	4349 (37)	2488 (21)	11797 (100)
Age, years (median, range)	51 (18-76)	52 (18-75)	54 (18-81)	53 (18-78)	52 (18-80)
Age < 40	458 (22)	654 (23)	941 (22)	569 (23)	2622 (22)
Age 40-49	480 (23)	652 (22)	768 (18)	487 (20)	2387 (20)
Age 50-64	964 (47)	1339 (46)	2059 (47)	1161 (47)	5523 (47)
Age ≥ 65	159 (8)	254 (9)	581 (13)	271 (11)	1265 (11)
Disease					
ALL	260 (13)	361 (12)	570 (13)	331 (13)	1522 (13)
AML	926 (45)	1317 (45)	1570 (36)	910 (37)	4723 (40)
CLL	76 (4)	113 (4)	354 (8)	184 (7)	727 (6)
CML	82 (4)	112 (4)	177 (4)	97 (4)	468 (4)
Hodgkin lymphoma	70 (3)	94 (3)	128 (3)	85 (3)	377 (3)
MDS	233 (11)	330 (11)	541 (12)	297 (12)	1401 (12)
Myeloproliferative neoplasms	75 (4)	95 (3)	146 (3)	77 (3)	393 (3)
Non-Hodgkin lymphoma	260 (13)	360 (12)	707 (16)	400 (16)	1727 (15)
Multiple myeloma	79 (4)	117 (4)	156 (4)	107 (4)	459 (4)
Disease risk index[a]					
Low	226 (11)	342 (12)	682 (16)	363 (15)	1613 (14)
Intermediate	1371 (67)	1866 (64)	2668 (61)	1495 (60)	7400 (63)
High	401 (19)	575 (20)	820 (19)	518 (21)	2314 (20)
Very high	63 (3)	116 (4)	179 (4)	112 (5)	470 (4)
HCT-CI[b]					
0	761 (37)	1143 (39)	1802 (41)	1035 (42)	4741 (40)
1-2	593 (29)	764 (26)	1224 (28)	735 (30)	3316 (28)
3+	681 (33)	956 (33)	1260 (29)	690 (28)	3587 (30)
Missing	26 (1)	36 (1)	63 (1)	28 (1)	153 (1)
Karnofsky performance score					
< 90	713 (35)	1027 (35)	1481 (34)	819 (33)	4040 (34)
90-100	1266 (61)	1754 (61)	2703 (62)	1553 (62)	7276 (62)
Missing	82 (4)	118 (4)	165 (4)	116 (5)	481 (4)
Donor match[c]					
MRD	998 (48)	1038 (36)	1492 (34)	1293 (52)	4821 (41)
Non-MRD					
8/8 HLA-match URD	672 (33)	1374 (47)	2119 (49)	727 (29)	4892 (41)
7/8 HLA-match URD	239 (12)	337 (12)	512 (12)	293 (12)	1381 (12)
Haploidentical relative	82 (4)	88 (3)	128 (3)	103 (4)	401 (3)
7/8 HLA-match relative	26 (1)	19 (<1)	34 (<1)	27 (1)	106 (1)
6/8 HLA-match URD	31 (2)	28 (<1)	43 (<1)	26 (1)	128 (1)
Matching unknown	13 (<1)	15 (<1)	21 (<1)	19 (<1)	68 (1)
Graft source					
Bone marrow	291 (14)	415 (14)	565 (13)	285 (11)	1556 (13)
Peripheral blood	1770 (86)	2484 (86)	3784 (87)	2203 (89)	10241 (87)
Conditioning regimen					
Myeloablative	1160 (56)	1645 (57)	2262 (52)	1341 (54)	6408 (54)
Reduced intensity	901 (44)	1254 (43)	2087 (48)	1147 (46)	5389 (46)
GvHD prophylaxis					
CnI + methotrexate	1156 (56)	1697 (59)	2449 (56)	1426 (57)	6728 (57)
CnI + mycophenolate	471 (23)	653 (23)	1053 (24)	600 (24)	2777 (24)
T-cell depletion	47 (2)	47 (2)	73 (2)	42 (2)	209 (2)
Post-transplant Cy	100 (5)	79 (3)	128 (3)	88 (4)	395 (3)
Other	287 (14)	423 (15)	646 (15)	332 (13)	1688 (14)
CMV serostatus					
R- /D-	472 (23)	688 (24)	1369 (31)	634 (25)	3163 (27)
R-/D+	233 (11)	271 (9)	484 (11)	374 (15)	1362 (12)
R+/D-	560 (27)	1021 (35)	1273 (29)	564 (23)	3418 (29)
R+/D+	756 (37)	859 (30)	1143 (26)	860 (35)	3618 (31)
Unknown	40 (2)	60 (2)	80 (2)	56 (2)	236 (2)

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Year of transplant					
2008	635 (31)	884 (30)	1311 (30)	758 (30)	3588 (30)
2009	691 (34)	981 (34)	1459 (34)	840 (34)	3971 (34)
2010	735 (36)	1034 (36)	1579 (36)	890 (36)	4238 (36)
Median follow up among survivors, months (range)	48 (12, 76)	48 (2.5, 75)	48 (3, 76)	48 (2.3, 76)	48 (2.3-76)

Numbers are frequencies with percentage in parenthesis except medians and ranges. Percentages may not add up to 100 because of rounding. [a]Classified according to Armand[18] et al. [b]Classified according to Sorror[22] et al. [c]Classified according to Lee[23] et al.; haploidentical category also includes 5/8 and 6/8 matched relatives. M–>M: male donor with male recipient; F–>M: female donor with male recipient; F–>M: female donor with male recipient; F–>F: female donor with female recipient. ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; CLL: chronic lymphocytic leukemia; CML: chronic myelogenous leukemia; MDS: myelodysplastic syndrome; HCT-CI: HCT comorbidity index; MRD: matched related donor; URD: unrelated donor; GvHD: graft-versus-host disease; CnI: calcineurin inhibitor; Cy: cyclophosphamide; CMV: cytomegalovirus.

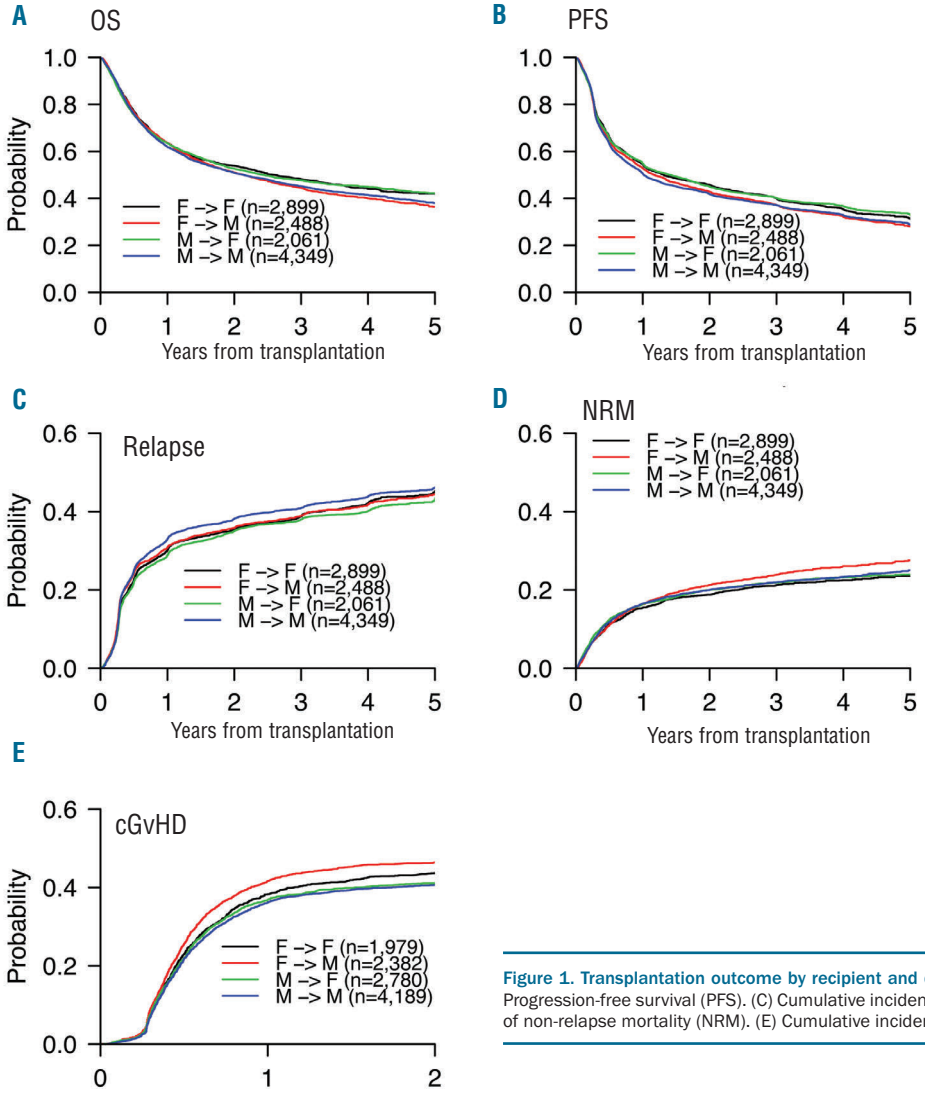

Figure 1. Transplantation outcome by recipient and donor sex. (A) Overall survival (OS). (B) Progression-free survival (PFS). (C) Cumulative incidence of relapse. (D) Cumulative incidence of non-relapse mortality (NRM). (E) Cumulative incidence of chronic GvHD.

M→M group, the HR was 1.03 (95%CI: 0.97-1.1, *P*=0.31) for OS and 0.99 (95%CI: 0.93-1.05, *P*=0.77) for PFS (Table 2B). Results were consistent when the analysis was repeated by disease (myeloid *vs.* lymphoid) (*data not shown*) or when the analysis was restricted to matched related or well matched unrelated (*data not shown*).

Relapse and non-relapse mortality

Relapse and NRM were slightly worse in male recipients compared with female recipients (Table 2A and *Online Supplementary Table S1*), but not significant at the 0.01 level. When sex combinations were considered, the 4-year cumulative incidence of NRM was 26% in the F→M group, 23% in each of the M→F, F→M, M→M groups (*P*=0.045 for the 4 group comparison, *P*=0.0075 for F→M *vs.* the other 3 groups combined) (Figure 1D, *Online Supplementary Table S1*) and the 4-year cumulative incidence of relapse was 44% in the M→M group, 40% in

Table 2A. Multivariable regression analysis* for overall survival, progression-free survival, relapse, non-relapse mortality and chronic graft-*versus*-host disease.

Recipient	OS				PFS				Relapse				NRM				cGvHD			
Sex	HR	95% CI		*P*	HR	95% CI		*P*	HR	95% CI		*P*	sHR	95% CI		*P*	sHR	95% CI		*P*
Male *vs.* female	1.11	1.05	1.16	<0.0001	1.10	1.05	1.15	<0.0001	1.06	1.002	1.12	0.04	1.09	1.01	1.17	0.032	1.02	0.96	1.08	0.47

Table 2B. Multivariable regression analysis* for OS, PFS, relapse, NRM, and cGVHD.

Donor and recipient																				
Sex	HR	95% CI		*P*	HR	95% CI		*P*	sHR	95% CI		*P*	sHR	95% CI		*P*	sHR	95% CI		*P*
F–>F *vs.* M–>F	1.02	0.94	1.10	0.64	1.02	0.95	1.10	0.58	1.02	0.93	1.11	0.66	1.02	0.90	1.15	0.78	1.11	1.01	1.21	0.023
M–>M *vs.* M–>F	1.10	1.03	1.17	0.0032	1.11	1.05	1.18	0.0004	1.12	1.04	1.20	0.0036	1.03	0.93	1.13	0.62	0.99	0.92	1.06	0.76
F–>M *vs.* M–>F	1.14	1.06	1.22	0.0004	1.10	1.03	1.18	0.0044	0.99	0.91	1.08	0.89	1.22	1.10	1.37	0.0003	1.21	1.12	1.32	<0.0001
F–>M *vs.* M–>M	1.03	0.97	1.10	0.31	0.99	0.93	1.05	0.77	0.89	0.82	0.96	0.0037	1.19	1.08	1.32	0.0005	1.23	1.13	1.33	<0.0001

**Models are stratified by conditioning intensity. Cox model was used for overall survival (OS) and progression-free survival (PFS). Fine and Gray model was used for cumulative incidence of relapse, non-relapse mortality (NRM) and chrnoic graft-*versus*-host disease (cGvHD). Variables included in each model are listed in Table 1, except year of transplant.*

M→F, 42% in F→F, and 42% in F→M (P=0.03 for the 4 group comparison, P=0.009 for M→M *vs.* the other 3 groups combined) (Figure 1C, *Online Supplementary Table S1*). These results were consistent in multivariable analysis with a subdistribution hazard ratio (sHR) of NRM 1.22 for F→M compared with M→F (P=0.0003) and 1.19 for F→M compared with M→M (P=0.0005); sHR of relapse 1.12 for M→M compared with M→F (P=0.0036) and 1.12 for M→M compared with F→M (P=0.0037) (sHR of relapse 0.89 for F→M compared with M→M) (Table 2B).

Acute graft-versus-host disease

Out of 11,797 patients, for 168 patients (1.4% male and 1.5% female recipients) information regarding acute GvHD was missing. Of the remaining 11,629 patients, 5003 patients (43%) developed grade II-IV acute GvHD, and 2086 (18%) developed grade III-IV acute GvHD. Of the 5003 patients with grade II-IV acute GvHD, for 2988 (60%) the onset date of acute GvHD was not available. This large amount of missing informative data precluded an analysis of acute GvHD in time-to-event analysis. In order to circumvent the informative missing data regarding onset date as well as the confounding factor of early death without developing acute GvHD, we performed a landmark analysis on the frequency of acute GvHD restricted to patients who were alive at day 100 of HSCT (n=10,184). Of the 10,184 patients included in the landmark analysis, 4413 (43%) developed grade III-IV acute GvHD. No combination of recipient and donor sex was significantly associated with an increased frequency of grade II-IV or III-IV acute GvHD (Table 3A). However, in multivariable logistic regression analysis, F→M had slightly higher odds of developing grade II-IV acute GvHD (OR 1.17, 95CI:1.04-1.32, P=0.01).

Chronic graft-versus-host disease

Among all the patients, 467 patients had missing onset date of chronic GvHD; the rate of missing information was similar across all recipient and donor sex combinations (approx. 4%). Among all patients with available information (n=11,330), when the cumulative incidence of chronic GvHD was compared by recipient and donor sex, there was a significant increase in the F→M group. The 1-year cumulative incidence rate in this group was 42% (P<0.0001), compared with 37% in M→F, 38% (P=0.14) in F→F, and 36% (P=0.79) in M→M (Table 3B and Figure 1E). This was confirmed in multivariable analysis with an sHR of 1.21 (P<0.0001) for F→M compared with M→F, 1.23 (P<0.0001) compared with M→M (Table 2B). Among female donors, the cumulative incidence of chronic GvHD in F→F was somewhat higher compared with M→F (sHR 1.11, P=0.023). Since graft source is a significant prognostic factor for chronic GvHD, we analyzed chronic GvHD by sex match and graft source. Again the F→M group had a higher incidence of chronic GvHD compared to the other three groups, regardless of the graft source (*Online Supplementary Table S2*).

Discussion

By analyzing a large cohort of patients undergoing allogeneic transplants from multiple centers in the modern transplantation era, we show that male recipients have worse OS and PFS compared to female recipients regardless of donor sex, with approximately a 10% relative increase in the hazard of death or death/relapse in multivariable analyses. The basis for the detrimental effect of male recipient sex appears to vary by donor sex. In F→M transplants, there is an increase in NRM, likely attributable to an increase in chronic GvHD. Despite this increase in NRM and chronic GvHD, we could not identify a decreased incidence of relapse in the F→M group compared with M→F, and the ultimate effect of this sex combination was a decrement in OS and PFS. When the F→M group was compared with the M→M group, there was no difference in OS and PFS, but a decrease in relapse and an increase in NRM and chronic GvHD. These results in F→M are largely consistent with previous studies.[2,3,5,7,9] Randolph *et al.*[2] proposed that F→M pairs have the lowest risk for relapse and the greatest odds for GvHD compared to other recipient and donor sex combination groups, suggesting a selective graft-*versus*-leukemia (GvL) effect in this cohort. However, the worst OS was seen in F→M, implying that the NRM was significantly higher in F→M than the other three groups in that cohort, which outweighed the benefit in terms of relapse.

In addition, we observed that M→M pairs have an increased incidence of relapse, compared to all of the other recipient and donor sex combination groups. There is no obvious biological basis for this result from our knowledge of Y chromosome mHAs unless Y chromosome itself attributes to this effect, as it has been seen in the general

Table 3A. Frequency of acute graft-*versus*-host disease (aGvHD): landmark analysis at day 100 post hematopoietic stem cell transplantation.

Donor and patient sex	N	II-IV aGvHD		III-IV aGvHD	
		N[a]	%	N[b]	%
M–>F	2468	1058	42.9	383	15.5
F–>F	1786	783	43.8	292	16.3
M–>M	3771	1602	42.5	603	16
F –>M	2159	970	44.9	356	16.5
P[c]		0.29		0.81	

[a]*Frequency of grade II-IV aGVHD;* [b]*frequency of grade III-IV aGVHD;* [c]*both P-values (0.29 and 0.81) are for the 4 group comparison. P-values for all pairwise comparisons were >0.1.*

Table 3B. Chronic graft-*versus*-host disease outcome by recipient and donor sex combination.

Donor and patient sex	N	Cumulative incidence		*P*
		1-year (95%CI)	2-year (95%CI)	
M–>F	2780	37% (35-39)	41% (39-43)	ref
F–>F	1979	38% (36-40)	44% (42-44)	0.14
M–>M	4189	36% (35-38)	41% (39-42)	0.79
F–>M	2382	42% (40-44)	46% (44-48)	<0.0001

population that males have a shorter life expectancy than females. The higher incidence of relapse seen in M→M resembles an increased relapse rate seen in matched sibling donors as compared to matched unrelated donors. We note, however, that the final outcome of these effects, namely an inferior OS and PFS in male recipients of HSCT compared to female recipients, regardless of donor sex, is consistent with that described in another large and fully disease risk-annotated HSCT cohort.[18] Nonetheless, one may argue that male recipients have higher risk baseline characteristics compared to female recipients. However, the distributions of DRI and HCT-CI are largely compatible across all recipient and donor sex combinations (Table 1), suggesting that female donors were not particularly used for high-risk male recipients. Given this, and the very large size of the present cohort, it seems highly unlikely that this is a statistical artifact. Instead, we hope that our findings can generate new biological studies of sex itself and sex-related mHAs to explain this phenomenon. As to sex mismatch for female recipients, donor sex has no effect on OS, PFS, relapse, and NRM, which is consistent with the result reported in Randolph *et al.*[2] but different from a previous EBMT report.[3] In their study, Gahrton *et al.*[3] reported that the F→F group had a significantly lower NRM compared with M→F and had the best OS among all recipient and donor sex combinations.

We acknowledge several important limitations of this work. First, it is retrospective in nature and therefore, like other retrospective studies, is subject to possible confounding factors, even though a sex-based selection bias seems unlikely. Second, about 4% of patients had missing onset date of chronic GvHD; as this percentage was similar across all sex combinations, the results should not be significantly affected. For acute GvHD, because the essential transplant data collection form does not mandate capturing the onset date of acute GvHD, a large portion of patients did not have this information, which precluded a time-to-event data analysis of this outcome. However, since most acute GvHD occur early after HSCT, and given that nearly all patients (>99.97%) were followed for at least six months, the landmark analysis we performed is unbiased and the results for group comparison should be consistent whether binary data analysis or time-to-event analysis is used, even though the overall incidence rates of acute GvHD may be slightly underestimated. The effect of donor parity and donor age on transplantation outcomes was not explored in the current analyses. Data on parity for sibling donors was not collected consistently during the study period, which prevented us from exploring any effects of parity in the setting of HLA-matched related donor HSCT. A recent report from our group on optimal donor characteristics for unrelated donor transplantation showed higher mortality risk with increasing donor age, higher NRM and fewer relapse with parous female donors.[24] However, parity was not associated with survival, as any advantage from lower relapse risk was negated by higher NRM.[24] The age of the sibling donor is tightly correlated with recipient age and was not examined further.

In summary, for female recipients of allograft, donor sex has no detectable effect on HSCT outcomes. In contrast, for male recipients, female donors are associated with a decreased incidence of relapse, an increased incidence of NRM and chronic GvHD, while male donors are associated with an increased incidence of relapse. As a result, both OS and PFS are significantly worse for all male recipients, regardless of donor sex. Furthermore, because OS and PFS are similar between F→M and M→M, one could argue that male recipients fare better with male donors considering the chronic GvHD related quality of life (QoL). However, it is not obvious whether QoL would be more severely affected by GvHD or by management of relapse, so that it may be premature to make recommendations about the preferred donor sex for male recipients until additional studies that include QoL are conducted. Finally, it is important to recognize that the absolute differences in clinical outcomes across recipient and donor sex combinations are small (within

5% across all sex combinations) and much smaller than those attributable to important prognostic factors such as disease risk index and donor-recipient HLA match. Nonetheless, our results do have a direct and important bearing on the choice of HSCT donors. In our cohort, the donor sex distribution seemed to be skewed toward male donors for male recipients (64% *vs.* 42% sex matched in female recipients), which may reflect the commonly held view that a male donor is preferable for a male recipient, which was perhaps derived from the clinical reports in previous years. However, based on our findings, recipient sex rather than donor sex appears to be the predominant prognostic driver. Consequently, donor sex should not be considered in the donor selection algorithm until we have a better insight into the biology of sex-based alloreactivity.

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