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ORIGINAL ARTICLE

# The negative impact of female donor/male recipient combination in allogeneic hematopoietic stem cell transplantation depends on disease risk

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**Conflicts of Interest**
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## Summary

Optimal donor selection is one of the key factors to enhance the success rate of allogeneic hematopoietic stem cell transplantation (HSCT). The effect of sex mismatch, especially the effect of Y chromosome mismatch in graft-versus-host disease (GVHD) direction (female donors to male recipients: denoted as FtoM mismatch) on overall survival (OS) has been controversial and not examined out of the patient population in Western countries. We retrospectively analyzed 225 cases of allogeneic HSCT and showed that FtoM mismatch confers a highly significant impact on OS ($P < 0.005$) in Japanese population. We demonstrated that this effect depends on the disease risk; for standard risk cases, this effect was significantly associated with poor outcome (for OS, $P = 0.021$), while for high risk cases, it had no effect on the results (for OS, $P = 0.26$). We further showed that FtoM mismatch was associated with nonrelapse mortality ($P = 0.019$) and most of them were GVHD-related in standard risk cases. In conclusion, FtoM mismatch has a significant impact on transplant outcome, especially in standard risk cases.

## Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) has been one of the most effective therapeutic modalities for patients with hematological malignancies and bone marrow failure syndromes. Although alloimmunity plays a pivotal role for successful HSCT through the eradication of the remaining tumor cells which is referred to as graft-versus-leukemia (GVL) effect, this reaction simultaneously operates to attack host organs, leading to treatment-related morbidities and mortalities known as graft-versus-host disease (GVHD). As severe GVHD impairs overall results, transplant physicians prefer donors who possess fewer factors associated with severe GVHD. In a large scale analysis of 6978 bone marrow transplantations facilitated by the National Marrow Donor Program (NMDP), female donors with multiple pregnancies were predictive of chronic GVHD [1]. The impact of donor and recipient sex and parity on HSCT outcomes was examined more closely in Centers for International Blood and Marrow Transplant Research (CIBMTR) registry consisting of 2626 cases donated from human leukocyte antigen (HLA)-identical donors [2]. Gahrton [3] reviewed the impact of donor and recipient sex combination in allogeneic HSCT for various hematopoietic diseases and reported that transplant-related mortality in female donor and male recipient combination is higher than in other combinations, which accounted for

poorer outcomes in this combination. It has been presumed that human minor histocompatibility antigens (mHAs) encoded on Y chromosome contribute to the allo-reactive immunogenicity in male recipients from female donors. Actually, several mHAs have been identified such as DBY [4], SMYC [5], UTY [6] and DFFRY [7] to elicit T-cell responses from female donors.

However, data about the clinical significance of sex mismatch is limited to Western population and few reports exist on Asian people [1–3,8–10]. We further examined whether the risk of underlying disease influences the impact of sex mismatch because there are several reports that the impact of GVHD-associated factors on clinical outcome is different between high and standard risk of the diseases [11]. In the current study, we demonstrated that the impact of sex mismatch, especially of FtoM (female donors to male recipient) mismatch, on clinical outcome of HSCT depends on the disease risk.

## Patients and methods

### Patients

From June 1995 to December 2007, we conducted allogeneic HSCT for 315 cases at Tokyo University Hospital. Among them, patients with acute leukemia, chronic myeloid leukemia (CML) and myelodysplastic syndrome (MDS) were enrolled in this study. Patients with aplastic anemia, lymphoma and other miscellaneous disorders were precluded from this study because risk stratification is not properly defined for these disorders. We also excluded 24 cases for which alemtuzumab was administered as GVHD prophylaxis for one-haplotype mismatched transplantation and eight cases of cord blood transplantation. Finally, we covered 225 cases and medical records were available for all of them. Detailed information of patients as separated by sex mismatch and disease risk is shown in Table 1. Acute leukemia in the first

**Table 1.** Characteristics of the patients. The basic characteristics of 225 patients included in this study.

| | Sex mismatch | | | Disease risk | | |
|---|---|---|---|---|---|---|
| | FtoM | Others | Significance (*P*-value) | Standard | High | Significance (*P*-value) |
| Age | | | | | | |
| Median | 41 | 39 | 0.36* | 37 | 40 | 0.22* |
| Range | 17–59 | 16–66 | | 16–66 | 17–63 | |
| Sex of patients | | | | | | |
| Male | 52 | 95 | | 60 | 87 | 0.035 |
| Female | 0 | 78 | | 44 | 34 | |
| Disease | | | | | | |
| AML | 24 | 54 | 0.079 | 26 | 52 | <0.0001 |
| ALL | 8 | 55 | | 40 | 23 | |
| CML | 11 | 37 | | 29 | 19 | |
| MDS | 9 | 27 | | 9 | 27 | |
| Disease risk | | | | | | |
| High | 32 | 89 | 0.21 | 0 | 121 | |
| Standard | 20 | 84 | | 104 | 0 | |
| Graft source | | | | | | |
| PB | 17 | 32 | 0.036 | 18 | 25 | 0.61 |
| BM | 35 | 141 | | 86 | 96 | |
| HLA matching | | | | | | |
| Match | 38 | 137 | 0.35 | 85 | 9 | 0.20 |
| Mismatch | 14 | 36 | | 19 | 31 | |
| Relationship between donor and patient | | | | | | |
| Related | 33 | 73 | 0.011 | 51 | 55 | 0.60 |
| Unrelated | 19 | 100 | | 53 | 66 | |
| Conditioning regimens | | | | | | |
| Full | 49 | 157 | 0.57 | 97 | 109 | 0.48 |
| Reduced | 3 | 16 | | 7 | 12 | |
| GVHD prophylaxis | | | | | | |
| CsA based | 47 | 155 | 1 | 100 | 102 | 0.0036 |
| FK-506 based | 5 | 18 | | 4 | 19 | |

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; PB, peripheral blood; BM, bone marrow; GVHD, graft-versus-host disease; CsA, cyclosporine A.
*Two-sided *t*-test.

complete remission (CR), CML in the first chronic phase, MDS in refractory anemia or refractory anemia with ringed sideroblasts were considered to be at standard risk. Acute leukemia beyond first CR, CML beyond first CP and MDS with excess of blasts was considered at high risk. This study was performed in accordance with the Helsinki Declaration and approved by the Ethics Committee of the University of Tokyo Hospital. All patients provided written informed consent for retrospective data exploitation.

### Transplant procedures

Myeloablative-conditioning regimen included 120 mg/kg cyclophosphamide (CY) combined with 12 Gy of total body irradiation (TBI) or 16 mg/kg of busulfan (BU). Cytosine arabinoside (CA) was added when relapse risk in central nervous system was assumed high. Patients with cardiac impairment received 40 mg/kg of CY and 40 mg/kg of VP-16 instead of the conventional dose of CY [12]. Nonmyeloablative-conditioning regimen typically consists of fludarabine and alkylating agents with or without low dose TBI. For GVHD prophylaxis, standard regimens consisting of short-term methotrexate (MTX) and calcineurin inhibitors (cyclosporine A or FK-506) were applied. Short-term MTX is principally composed of MTX at 10, 7, 7 mg/m$^2$ on day 1, 3, 6, respectively, for HLA-matched related donors. Additional MTX at 7 mg/m$^2$ on day 11 was applied for unrelated or HLA-mismatched donors, and MTX at 15, 10, 10, 10 mg/m$^2$ on day 1, 3, 6, 11 was applied only for HLA-class I mismatched unrelated donors. Minor modifications for short-term MTX schedule were applied to this policy if patients were enrolled in clinical studies. Acute GVHD was graded according to the established criteria. Severe acute GVHD (grade II or higher) was treated with intravenous prednisolone at least 1 mg/kg except stage 3 skin GVHD was the only manifestation. If response was observed, prednisolone was tapered gradually.

### Statistical analysis

Older age was defined to be older than 50 years old. Sex mismatch was dichotomously divided into FtoM arm and the others (Others) arm. HLA mismatch indicates having one or more genotypic mismatch in HLA-A, HLA-B, or HLA-DRB1 loci, and HLA match indicates genotypically identical in 6/6 loci. Fischer's exact test was used to assess the difference in categorical variables between the two groups. The two-sided *t*-test was used to compare the continuous variables between the two groups. The Kaplan–Meier method was employed to estimate the overall survival (OS) and relapse-free survival (RFS). The difference of survival curves was assessed with log-rank test. Competing risk analysis was applied for estimation of relapse and nonrelapse mortality (NRM) assuming each other as competing risks. For GVHD, death from any cause and relapse were considered competing events. The Cox proportional hazard model was used to evaluate the effect of multiple covariates. Factors that showed at least weak association ($P < 0.10$) in the univariate analyses (Table 2) and sex combination were included in the multivariate analyses. Competing risk regression model was applied to conduct regression modeling of sub-distribution functions in competing risks. The statistical package R 2.6.1 (The R Foundation for Statistical Computing, Vienna, Austria, 2007. http://www.R-project.org/) was used for data management and analysis.

## Results

### Patient characteristics

The median time of observation was 67 months (range: 7–162) after HSCT. The distribution of sex combination of donors and recipients were as follows; 35 female to female, 52 female to male, 43 male to female, and 95 male to male cases. Hence, all the patients were grouped into 52 FtoM arm and 173 Others arm. The composition of FtoM and Others arm was not equivalent between related and unrelated transplantation cases ($P = 0.011$). There were no significant differences of disease risk ($P = 0.21$), graft source ($P = 0.11$), HLA parity between donor and recipient ($P = 0.35$), intensity of conditioning regimens ($P = 0.57$), GVHD prophylaxis ($P = 1.00$) and age distribution ($P = 0.36$) between FtoM and Others arms (Table 1).

### Survival

The OS and RFS based on FtoM mismatch or Others are shown in Fig. 1a and b, respectively. The effect of FtoM mismatch was evident for both OS [hazard ratio (HR): 1.84; 95% confidential interval (CI): 1.2–2.7, $P = 0.0024$] and RFS (HR: 1.90; 95% CI: 1.3–2.8, $P = 0.0011$). This trend was constantly observed when cases were stratified by the underlying disease (data not shown). Next, we examined whether disease stage at transplantation has any impact on the influence of FtoM mismatch. According to the criteria determined in Patients and methods section, 121 cases were ranked as high risk and 104 cases as standard risk. In high risk patients, neither OS nor RFS varied significantly according to FtoM mismatch (OS: $P = 0.20$, Fig. 2a; RFS: $P = 0.22$, Fig. 2b). By contrast, in standard risk cases, FtoM combination significantly predicted unfavorable outcome for both OS ($P = 0.011$, Fig. 2c) and RFS ($P = 0.0020$, Fig. 2d). With univariate analysis (Table 2), the unfavorable factors that affected OS were

the risk of the disease (HR: 3.76, $P < 0.0001$), the underlying disease other than CML (HR: 0.593, $P = 0.04$), peripheral blood graft source (HR: 1.90, $P = 0.0045$), applying reduced-intensity regimen (HR: 2.43, $P = 0.0021$) and FtoM combination (HR: 1.84, $P = 0.0028$). Similarly, factors that were associated with poorer RFS were the risk of the disease (HR: 3.59, $P < 0.0001$), peripheral blood graft source (HR: 1.74, $P = 0.014$), applying reduced-intensity regimen (HR: 2.33, $P = 0.0024$) and FtoM combination (HR: 1.90, $P = 0.0013$). We next applied multivariate analyses using variables that showed significant or sub-significant correlation with outcomes and sex combinations. Factors that predicted poor OS were high disease risk (HR: 4.0, $P < 0.001$), applying reduced-intensity regimen (HR: 2.4, $P = 0.0036$), using peripheral blood stem cells (HR: 1.7, $P = 0.018$) and FtoM combination (HR: 1.6, $P = 0.028$). Factors that were associated with poor RFS were high disease risk (HR: 3.6, $P < 0.001$), applying reduced-intensity regimen (HR: 2.2, $P = 0.0059$), and FtoM combination (HR: 1.5, $P = 0.036$). In a subgroup of the standard risk cases, FtoM combination was the only significant factor that predicted poorer OS (HR: 2.82, $P = 0.012$) and RFS (HR: 3.61, $P = 0.0016$) in multivariate analysis.

**Table 2.** Univariate analysis for OS and RFS. Hazard ratios (HR) with 95% confidential interval (CI) are shown for OS (A) and RFS (B).

**(A)**

| | | OS | | |
|---|---|---|---|---|
| | *N* | HR | 95% CI | *P*-value |
| Age (years) | | | | |
| <50 | 183 | 1 | – | – |
| ≥50 | 42 | 1.23 | 0.77–1.96 | 0.39 |
| Underlying disease | | | | |
| AML | 78 | 1 | – | – |
| ALL | 63 | 0.922 | 0.60–1.41 | 0.71 |
| CML | 48 | 0.593 | 0.36–0.98 | 0.04 |
| MDS | 36 | 1.14 | 0.88–1.89 | 0.61 |
| Disease risk | | | | |
| Standard | 104 | 1 | – | – |
| High | 121 | 3.76 | 2.44–5.80 | <0.001 |
| Graft source | | | | |
| Bone marrow | 182 | 1 | – | – |
| Peripheral blood | 43 | 1.9 | 1.22–2.97 | 0.0045 |
| HLA matching | | | | |
| Match | 175 | 1 | – | – |
| Mismatch | 50 | 1.39 | 0.91–2.12 | 0.12 |
| Relationship | | | | |
| Related | 106 | 1 | – | – |
| Unrelated | 119 | 0.734 | 0.50–1.07 | 0.11 |
| Conditioning regimen | | | | |
| Conventional | 206 | 1 | – | – |
| Reduced | 19 | 2.43 | 1.38–4.29 | 0.0021 |
| GVHD prophylaxis | | | | |
| CsA based | 202 | 1 | – | – |
| FK-506 based | 23 | 1.43 | 0.83–2.47 | 0.2 |
| Sex combination | | | | |
| Others | 173 | 1 | – | – |
| Females to males | 52 | 1.84 | 1.23–2.74 | 0.0028 |

**Table 2.** *continued*

**(B)**

| | | RFS | | |
|---|---|---|---|---|
| | *N* | HR | 95% CI | *P*-value |
| Age (years) | | | | |
| <50 | 183 | 1 | – | – |
| ≥50 | 42 | 1.17 | 0.74–1.84 | 0.51 |
| Underlying disease | | | | |
| AML | 78 | 1 | – | – |
| ALL | 63 | 1.13 | 0.59–1.35 | 0.58 |
| CML | 48 | 0.72 | 0.45–1.14 | 0.16 |
| MDS | 36 | 1.00 | 0.60–1.65 | 1.00 |
| Disease risk | | | | |
| Standard | 104 | 1 | – | – |
| High | 121 | 3.59 | 2.37–5.43 | <0.001 |
| Graft source | | | | |
| Bone marrow | 182 | 1 | – | – |
| Peripheral blood | 43 | 1.74 | 1.12–2.70 | 0.014 |
| HLA matching | | | | |
| Match | 175 | 1 | – | – |
| Mismatch | 50 | 1.28 | 0.84–1.93 | 0.25 |
| Relationship | | | | |
| Related | 106 | 1 | – | – |
| Unrelated | 119 | 0.72 | 0.50–1.05 | 0.085 |
| Conditioning regimen | | | | |
| Conventional | 206 | 1 | – | – |
| Reduced | 19 | 2.33 | 0.43–1.35 | 0.0024 |
| GVHD prophylaxis | | | | |
| CsA based | 202 | 1 | – | – |
| FK-506 based | 23 | 1.35 | 0.78–2.32 | 0.28 |
| Sex combination | | | | |
| Others | 173 | 1 | – | – |
| Females to males | 52 | 1.90 | 1.29–2.82 | 0.0013 |

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; HLA, human leukocyte antigen; GVHD, graft-versus-host disease; CsA, cyclosporine A.

### Causes of failure from RFS

To further examine the reasons that explain the different impact of sex combination on RFS between different risk groups, we analyzed relapse and NRM rates assuming that each is a competing event to each other. In the standard risk group, the relapse rate was not significantly different between the FtoM and Others arms ($P = 0.24$, Fig. 3a). By contrast, NRM was more frequent in the FtoM arm than in the Others arm ($P = 0.017$, Fig. 3b). On the other hand,

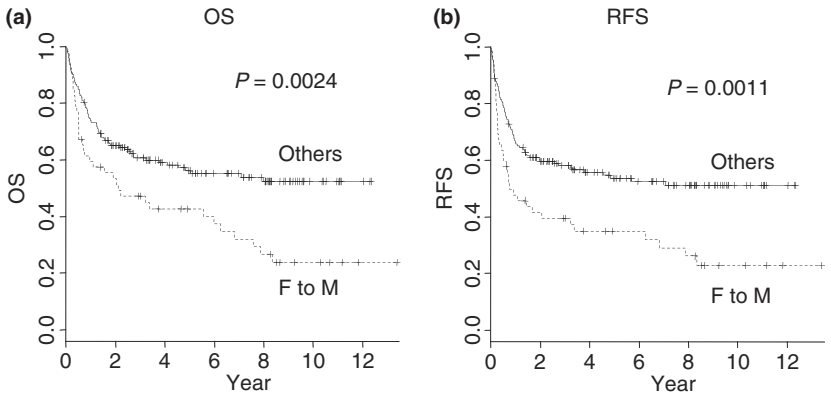


**Figure 1** Survival curves for patients with different donor/recipient sex groups. Overall survival (OS) (a) and relapse-free survival (RFS) (b) were estimated using Kaplan–Meier method and compared between FtoM (female donors to male recipients) and Others groups. *P*-values indicate the statistical significance of the difference of outcome by log-rank test.

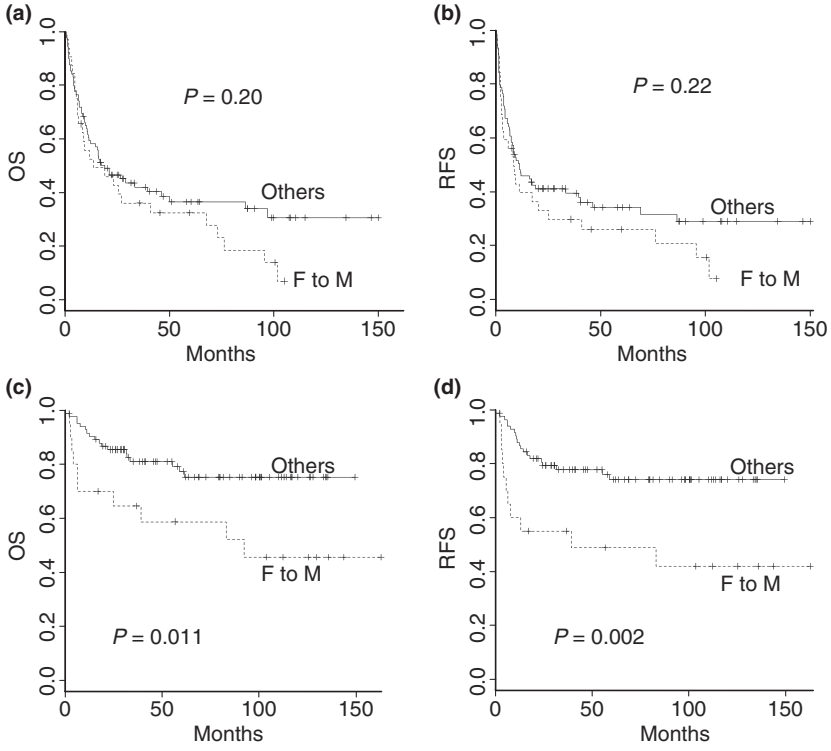


**Figure 2** Survival curves for patients with different sex mismatch for different disease risk. Overall survival (a, c) and relapse-free survival (RFS) (b, d) were calculated and shown by Kaplan–Meier method for high risk (a, b) and standard risk (c, d) cases. *P*-values indicate the statistical significance of the difference of outcome by log-rank test (FtoM, female donors to male recipients).

FtoM combination had no effect on both relapse ($P = 0.78$, Fig. 3c) and NRM ($P = 0.66$, Fig. 3d) in the high risk group. From this analysis, it follows that the reason for poor outcome in FtoM arm in standard risk patents is the high NRM. Neither relapse rate ($P = 0.78$) nor NRM ($P = 0.66$) was significantly different between FtoM and Others group in high risk patients.

Next, we explored the factors that explain high NRM in FtoM arm in standard risk cases. GVHD is the leading cause of NRM in allogeneic HSCT, and because previous reports have suggested that FtoM mismatch confers the higher risk of GVHD, we estimated the incidence of acute GVHD. Although the cumulative incidence of grade II to IV acute GVHD was slightly higher in FtoM than in

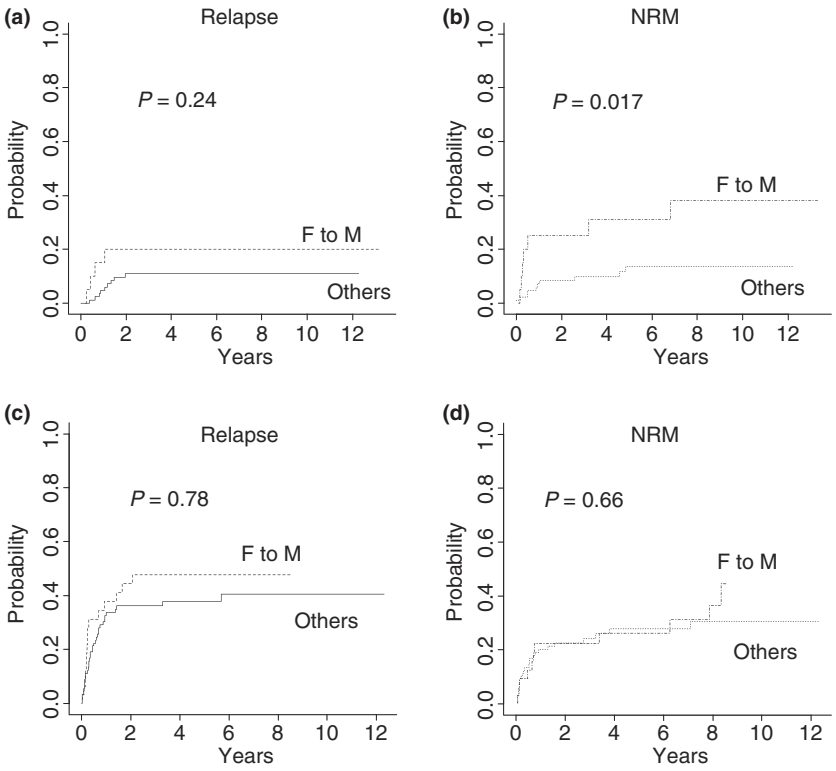


**Figure 3** The cumulative incidence for relapse and nonrelapse mortality (NRM). Cumulative incidence curves for relapse (a, c) and NRM (b, d) in the standard risk (a, b) and high risk (c, d) groups are shown considering with each other a competing event (FtoM, female donors to male recipients).

Others arms (overall: 60.0% vs. 48.6%, $P = 0.34$; high risk: 78.1% vs. 58%, $P = 0.052$; standard risk: 39% vs. 30%, $P = 0.46$), severe acute GVHD (grade III to IV) tended to occur more frequently in the FtoM arm (overall: 15% vs. 6.3%, $P = 0.09$; high risk: 19% vs. 11%, $P = 0.35$; standard risk: 10% vs. 2.3%, $P = 0.15$). The cumulative incidence of chronic GVHD of day 100 survivors were also similar between FtoM and Others groups (overall: 43.7% vs. 38.0%, $P = 0.46$; high risk: 40.2% vs. 50.4%, $P = 0.61$; standard risk: 36% vs. 33%, $P = 0.92$). Next, we examined the death cause closely. There were 17 NRM cases in the standard risk group and 35 in the high risk group. In the FtoM arm, 56% (10 out of 18 cases) died of GVHD or infection during steroid therapy for severe GVHD, while 32% (11 out of 34 cases) died of GVHD or associated diseases ($P = 0.14$) in the Others arm.

## Discussion

In our analysis, we showed that the impact of FtoM mismatch is larger than that reported before. Kallman *et al.* [1] reported that sex mismatch has no impact on survival as a result of the retrospective analysis of 6978 transplants in NMDP, and this was followed by a detailed analysis by Lee *et al.* [13] also using NMDP registry data in which sex mismatch has almost no impact on survival in HLA 8/8 matched transplants. Larger analysis from EBMT showed that FtoM combination had negative impact on survival, however, the relative risk was as small as 1.10 [8]. By contrast, the effect of FtoM mismatch was more evident for both OS (HR: 1.84; 95% CI: 1.2–2.7, $P = 0.0024$) and RFS (HR: 1.90; 95% CI: 1.3–2.8, $P = 0.0011$) in our analysis. We consider that this difference is based on the much less incidence of GVHD in Japanese populations than in Western races. This difference has been attributed to genetic homogeneity of the former, which is translated into less number of significant mHAs in Japanese population. To avoid increased relapses associated with lower GVHD incidence, many Japanese facilities, including ours, adopt reduced GVHD prophylaxis [14] from those applied in Western countries [15]. HSCT from a female donor to a male recipient is a special circumstance in which donor T cells that are specific for mHAs on Y chromosome may make a contribution to GVHD or GVL [9]. Concretely, such antigens

including DBY, UTY, DFFRY and SMCY have been identified through MHC class I or class II restricted mHAs [4–7]. These mHAs are different from other mHAs in that they are intrinsic to the genetic difference between X and Y chromosomes and this makes these mHAs unique in that their varieties are independent of the genetic heterogeneity in a population. This may have highlighted the effect of FtoM mismatch in the Japanese population where reduced GVHD prophylaxis is usually applied.

Our results show that the impact of FtoM mismatch depends on the risk of underlying diseases and that the scale of this impact is rather large in standard risk patients [HR; 3.0 (95% CI: 1.3–7.0) for OS and 3.4 (95% CI: 1.5–7.7) for RFS, both with multivariate analysis]. By contrast, FtoM mismatch has little effect on outcome in high risk cases. There are several reports regarding the effect of sex combination of donors and recipients on HSCT outcome [1,2,8–10]. In most of them, FtoM mismatch has been shown to exacerbate acute and/or chronic GVHD [1,2,9,16–18]. Our result also supported that FtoM mismatch is associated with increased risk of GVHD, especially of grade III to IV, although not statistically significant due to small number of patients. Predisposition toward GVHD-associated causes of NRM in the FtoM group indicates that GVHD cases in this group were severe.

This analysis poses many issues regarding optimal selection of donors. The straightforward interpretation of our result is that male donors should be preferred to female donors for male patients at standard risk if other conditions are equal. However, it is rare to have more than one HLA-identical sibling donors due to the recent trend toward fewer children in a family in advanced countries.

Another plausible application of our result other than donor selection is to employ more potent GVHD prophylaxis for FtoM combinations if the disease risk is standard. In this risk group, it is expected that the merit of suppressing GVHD and ameliorating NRM would overweigh the risk of increasing the probability of relapse [11]. Although we could not show that acute or chronic GVHD is significantly increased in FtoM arm, more death causes in this arm were associated with GVHD-related pathophysiology, indicating that GVHD impairs the outcome in this arm. So, we consider that the reason for different effect sizes of FtoM mismatch by disease risk is the balance of adverse effects of GVHD and beneficial effects of GVL. For a high risk male recipient, GVL effect of HSCT from female donor offsets the unfavorable effect of GVHD. On the other hand, when a female donor is selected for a standard risk male patient, the merit of GVL effect is limited and outweighed by the exacerbating effect of GVHD leading to poor outcome.

However, this study suffers from its retrospective nature and small number of patients. A large scale study to assess the relative significance of multiple factors that affects HSCT outcome including FtoM mismatch is warranted in non-Western population.

## Authorship

YN: designed the study, collected the data, analyzed the data and wrote the paper. KK: collected the data. AH, YI and TT: made substantial contribution to clinical practice. MK: supervised the study.

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