Title

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?

Journal

Transplantation and Cellular Therapy, 21(4)

Authors

Di Stasi, Antonio
Rondon, Gabriela
Chen, Julianne
et al.

Publication Date

2015-04-01

DOI

10.1016/j.bbmt.2014.12.018

Peer reviewed

HHS Public Access

Author manuscript

Biol Blood Marrow Transplant. Author manuscript; available in PMC 2016 April 01.

Published in final edited form as:

Biol Blood Marrow Transplant. 2015 April ; 21(4): 713–719. doi:10.1016/j.bbmt.2014.12.018.

Can a Female Donor for a Male Recipient Decrease Relapse Rate for Patients with AML Treated with Allogeneic Hematopoietic Stem Cell Transplantation?

Piyanuch Kongtim[1], **Antonio Di Stasi**[1], **Gabriela Rondon**[1], **Julianne Chen**[1], **Kehinde Adekola**[1], **Uday Popat**[1], **Betul Oran**[1], **Partow Kebriaei**[1], **Borje S. Andersson**[1], **Richard E. Champlin**[1], and **Stefan O. Ciurea**[1]

[1]Department of Stem Cell Transplantation and Cellular Therapy, the University of Texas MD Anderson Cancer Center, Houston, TX

Abstract

The mismatched minor histocompatibility antigens present on Y chromosome (H-Y) in male recipients receiving stem cells from female donors may contribute to graft-versus-leukemia effect (GVL) and results in reduce relapse rate especially in patients with high-risk disease. We retrospectively compared the outcomes of male AML patients 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 18–74 years). For the whole group, the one-year cumulative incidence of relapse was significantly lower in F-M group (34.1% versus 41.3%, p=0.044) while non-relapse mortality (NRM) was higher (23.2% versus 15.7%, p=0.004). 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=0.045) whereas NRM was not significantly different (35.8% versus 25.5%, p=0.141). Although survival was not significantly improved, transplantation from a female donor for male recipient was associated with a lower relapse rate. When relapse is most common concern for treatment failure, especially for younger patients, a female donor for a male recipient might be beneficial to decrease relapse rate post-transplant. Future studies are needed to explore how H-Y mismatch may improve survival post-transplant.

Correspondence to: Stefan O. Ciurea, M.D., Associate Professor, The University of Texas MD Anderson Cancer Centre, 1515 Holcombe Blvd., Unit 423, Houston, Texas, 77030. Phone: 713-745-0146, Fax: 713-794-4902, sciurea@mdanderson.org.

Authorship Contributions

PK: contributed with data collection and interpretation, performed the statistical analysis, and wrote the manuscript; AD, GR and JC collaborated in data collection and verification; KA, UP, BO, PK, BA provided patient care and data analysis; REC and SOC provided patient care, formulated the hypothesis, contributed to data analysis and writing of the manuscript. All the authors, read, reviewed and approved the final version of the manuscript.

Disclosure of Conflicts of Interest

The authors have no conflict of interests to declare.

Keywords

Minor histocompatibility antigens; graft-versus-host disease; graft-versus-leukemia effect; hematopoietic stem cell transplantation; busulfan conditioning

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) represents a potential 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 (mHAGs) present on the surface of leukemic cells.(1, 2) Unfortunately, since some of these antigens are also expressed on recipient's non-hematopoietic cells, alloreactivity against recipient's tissues can lead to a potential fatal complication, graft-versus-host disease (GVHD). One of the mHAGs 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 transplant-related mortality and incidence of GVHD in aplastic anemia patients who received a gender-mismatched as compared with gender-matched transplant.(3) Later, several studies demonstrated that HSCT from female donors to male recipients (F–M) as compared to 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, due to conflicting reports published to date.(4–7) Moreover, no data exists 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 benefit form a stronger antitumor effect generated by using a female donor instead of the traditional male donor, when this option is available, and retrospectively analyzed the impact of donor-recipient gender mismatch on transplant 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 transplant outcomes of all 841 patients, 18 years or older (456 male, 385 female) with diagnosis of AML who received their first transplant from an HLA matched related or 8/8 matched unrelated donor (MUD) at The University of Texas MD Anderson Cancer Center (MDACC) between January 1991–June 2012. Clinical data were gathered at the time of transplant. The median interval from diagnosis to transplant was 8 months (range 1–332 months); 453 (53.9%) and 388 patients (46.1%) received a transplant from matched related donor (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%), while 53 patients (6.3%) received a reduced-intensity conditioning regimen (RIC) with lower busulfan doses (AUC 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), non-relapse 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 0.5×10^9/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 WHO 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 & 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 ($p<0.1$) 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 (IRB) of the MDACC approved the treatment protocols and this retrospective study. All patients provided written informed consent for transplant according to the Declaration of Helsinki.

Results

Patients' characteristics are listed in Table 1. The median age was 50 years (range 18–74 years). All 841 patients had *de novo* AML except 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 MRC classification (13) and 561 patients (66.7%) were in remission prior to transplant. Cytogenetics and molecular data according to 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 F-M and OGC group, except there were more patients with secondary AML in the F-M group (22.9% versus 16.4%; p=0.018). Sixty-one patients (35.1%) in F-M group and 237 patients (35.5%) in OGC group had high-risk cytogenetic (p=0.652). Fifty-three patients (30.4%) in F-M group and 227 patients (34%) in OGC group underwent transplantation with active disease (p=0.479). Eight hundred and eighteen patients (97.3%) engrafted the donor cells (96% in F-

M group and 97.6% in OGC group (p=0.397) 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 F-M and OGC group (p=0.57). At the time of last follow up, 387 (46%) patients were alive with median follow up duration of 35 months (range 3–241 months). Transplant outcomes are summarized in Table 2.

Relapse

The CIR at 1 year for the entire cohort was 39.9%. When compared with OGC, patients in F-M group had lower relapse rate with CIR at 1 year of 34.1% versus 41.3% in OGC group (p=0.044). This difference was related to a significantly lower relapse rate for patients beyond 1st CR prior to transplant with 1-year CIR of 39.8% in F-M group versus 52% in OGC group respectively (p=0.039) while the patients who underwent HSCT in 1st CR had similar CIR (27.7% in F-M group, 31.2% in OGC, p=0.419). We then analyzed CIR of a subgroup of the patients who were not in 1st 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 F-M group (42.5%) as compared to OGC group (55.2%) (p=0.045) (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 prior to transplant, received myeloablative conditioning, peripheral blood stem cells, and 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 complete remission at transplant, transplant using RIC, and the presence of mixed donor-recipient chimerism early post-transplant, while having chronic GVHD was associated with 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 HR of 0.71 (95%CI 0.47–0.91, p=0.04).

Non-relapse mortality

Non-relapse mortality 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 OGC group with 1-year NRM of 23.2% versus 15.7% respectively (p=0.004). When compared with OGC, F-M group had higher incidence of fatal acute GVHD (8.5% versus 2.3%, p=0.031), chronic GVHD (7.1% versus 1.4%, p=0.027) and death from infections (11.6% versus 2.4%, p=0.025).

Again, the statistically significance was seen in subgroup patients who were not in 1st CR prior to HSCT (29.1% in F-M group versus 17.4% in OGC group, p=0.004) whereas the patients who were transplanted in 1st CR had comparable NRM (17.2% in F-M group versus 13.5% in OGC group, p=0.258). However, for patients younger than 50 years beyond 1st CR the NRM was not significantly different (35.8% in F-M group versus 25.5% in OGC group, p=0.141) (Figure 1B). These results suggest that this subgroup of patients might benefit

from a gender mismatched transplant (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 prior to 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 1st CR prior to transplant, and the development of acute GVHD (Table 4). All of these factors as well as transplant in male patients using stem cells from female donors retained their prognostic significance in multivariate analysis (Table 5).

Graft versus host disease

Although the cumulative incidence of all grades acute GVHD was comparable between the F-M (51.1%) and OGC group (50.4%), (p=0.691), grade 3–4 acute GVHD was significantly higher in F-M group (10.3% versus 5.8%, p=0.042). A higher incidence of severe acute GVHD (grade 3–4) was also seen in patients beyond 1st CR prior to transplant (16% in F-M group versus 8% in OCG group, p=0.036). Moreover, in patients beyond 1st CR who were younger than 50 years, the cumulative incidence of grade 3–4 acute GVHD had a trend to be higher in F-M group (17.4% in F-M group versus 7.7% in OGC group, p=0.055). 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=0.132). However, a higher incidence of chronic extensive GVHD was found in F-M group than those in OGC group (34.5% versus 26.5%, p=0.047).

Survival

The benefit of GVL effect resulted in lower relapse rate in F-M group. However, because of higher NRM related primarily to a higher incidence of acute GVHD grade 3–4 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 F-M group versus 38.3% in OGC group; p=0.943).

Three-year OS of the whole cohort was 43.9%. Again, there was no significant difference in OS of F-M and OGC group. Three-year OS was 43.4% in F-M group versus 44% in OGC group, p=0.449) (Table 2). The similar PFS and OS of all donor-recipient gender combinations were also seen in subgroup of the patients in 1st CR, or beyond 1st CR. The PFS and OS were also similar even for patients beyond 1st 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 risk of 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 1st CR prior to transplant, the use of a RIC regimen, mixed donor-recipient chimerism early post-transplant, 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 1st CR and the development of cGVHD while 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 demonstrated clearly that male patients with AML had lower relapse rate when received a gender mismatch transplant. These beneficial effects were in general offset by a higher treatment-related mortality related by higher incidence of GVHD and, overall similar survival outcomes. These findings raise the question if there is a group of patients who will benefit for 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 transplant and risk of NRM has been reported in several other studies (4, 7, 15, 16). In a retrospective EBMT analysis on patients with leukemia (including 1405 patients with AML), the authors showed that female donors to male recipients as compare to OGC significantly influenced risk of NRM in both AML and 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 F-M compared with the OGC group but only in patients beyond 1st CR, while NRM for patients transplanted in 1st CR were not different. This higher NRM in F-M was paralleled by higher incidence of grade 3–4 acute GVHD as well as chronic extensive GVHD. These findings suggests that mismatch in minor histocompatibility antigens located on 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 HR 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 influence NRM in F-M transplantation and the relationship with the development of GVHD remain to be clarified.

The minor histocompatibility antigens on 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 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 than female recipients with 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 statistical significant difference was seen only in patients with CML, while 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 due to an increased risk of NRM. Consequently, we have tried to identify a group of patients who might have a survival benefit from stronger GVL effect using a female donor. Male patients younger than 50 years with high-risk disease (who underwent transplant beyond 1st 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 transplant outcomes of F-M and OGC in 53,988 patients with hematologic malignancies (including 3701 AML patients) from EBMT. 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, $p<0.001$). However, when the analyses were done for each type of leukemia separately, the significant difference was seen in CML (48% versus 55.4%, $p<0.001$) and trend was noted for patients with AML (44.4% versus 46.2%, $p=0.07$), while OS of F-M and OGC were comparable in patients with ALL (40.9% vs 41.9%, $p=0.54$) (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 (DLI) 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 transplant. 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, like 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Feng X, Hui KM, Younes HM, Brickner AG. Targeting minor histocompatibility antigens in graft versus tumor or graft versus leukemia responses. Trends in immunology. 2008; 29(12):624–32. [PubMed: 18952501]
2. Horowitz MM, Gale RP, Sondel PM, Goldman JM, Kersey J, Kolb HJ, et al. Graft-versus-leukemia reactions after bone marrow transplantation. Blood. 1990; 75(3):555–62. [PubMed: 2297567]
3. Storb R, Prentice RL, Thomas ED. Treatment of aplastic anemia by marrow transplantation from HLA identical siblings. Prognostic factors associated with graft versus host disease and survival. The Journal of clinical investigation. 1977; 59(4):625–32. [PubMed: 14972]
4. Randolph SS, Gooley TA, Warren EH, Appelbaum FR, Riddell SR. Female donors contribute to a selective graft-versus-leukemia effect in male recipients of HLA-matched, related hematopoietic stem cell transplants. Blood. 2004; 103(1):347–52. [PubMed: 12969970]
5. Gahrton G, Iacobelli S, Apperley J, Bandini G, Bjorkstrand B, Blade J, et al. The impact of donor gender on outcome of allogeneic hematopoietic stem cell transplantation for multiple myeloma: reduced relapse risk in female to male transplants. Bone marrow transplantation. 2005; 35(6):609–17. [PubMed: 15696179]
6. Gratwohl A, Hermans J, Niederwieser D, van Biezen A, van Houwelingen HC, Apperley J. Female donors influence transplant-related mortality and relapse incidence in male recipients of sibling blood and marrow transplants. The hematology journal : the official journal of the European Haematology Association / EHA. 2001; 2(6):363–70. [PubMed: 11920275]
7. Stern M, Passweg JR, Locasciulli A, Socie G, Schrezenmeier H, Bekassy AN, et al. Influence of donor/recipient sex matching on outcome of allogeneic hematopoietic stem cell transplantation for aplastic anemia. Transplantation. 2006; 82(2):218–26. [PubMed: 16858285]
8. Ciurea SO, Andersson BS. Busulfan in hematopoietic stem cell transplantation. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2009; 15(5):523–36.
9. de Lima M, Couriel D, Thall PF, Wang X, Madden T, Jones R, et al. Once-daily intravenous busulfan and fludarabine: clinical and pharmacokinetic results of a myeloablative, reduced-toxicity conditioning regimen for allogeneic stem cell transplantation in AML and MDS. Blood. 2004; 104(3):857–64. [PubMed: 15073038]
10. Swerdlow, SHCE.; Harris, NL., et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 2008.
11. Cox D. Regression models and life tables (with Discussion). Journal of the Royal Statistical Society. 1972; (34):187–200.
12. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association. 1999; 94(446):496–509.
13. Grimwade D, Walker H, Oliver F, Wheatley K, Harrison C, Harrison G, et al. The importance of diagnostic cytogenetics on outcome in AML: analysis of 1,612 patients entered into the MRC AML 10 trial. The Medical Research Council Adult and Children's Leukaemia Working Parties. Blood. 1998; 92(7):2322–33. [PubMed: 9746770]
14. Dohner H, Estey EH, Amadori S, Appelbaum FR, Buchner T, Burnett AK, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood. 2010; 115(3):453–74. [PubMed: 19880497]
15. Frassoni F, Labopin M, Gluckman E, Prentice HG, Vernant JP, Zwaan F, et al. Results of allogeneic bone marrow transplantation for acute leukemia have improved in Europe with time–a report of the acute leukemia working party of the European group for blood and marrow transplantation (EBMT). Bone marrow transplantation. 1996; 17(1):13–8. [PubMed: 8673048]

16. Stern M, Brand R, de Witte T, Sureda A, Rocha V, Passweg J, et al. Female-versus-male alloreactivity as a model for minor histocompatibility antigens in hematopoietic stem cell transplantation. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2008; 8(10):2149–57.

Highlights

- HSCT using female donor to male recipient is associated with decrease relapse rate, yet higher NRM.
- Overall, a female donor was not associated with improved survival for AML patients
- Younger male patients with high risk AML may benefit from using stem cell from female donors

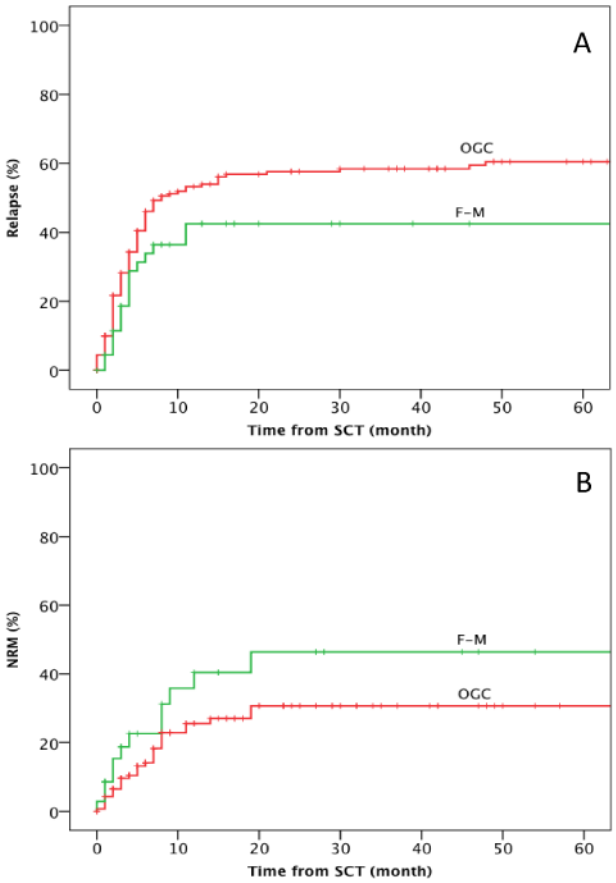

Figure 1.

Cumulative incidence of relapse (CIR) (A) and Non-relapse mortality (NRM) (B) of patients beyond 1st CR younger than 50 years

Biol Blood Marrow Transplant. Author manuscript; available in PMC 2016 April 01.

Table 1

Patient and transplant characteristics

Outcomes (%)	All patients			1st CR			Beyond 1st CR			Beyond 1st CR, <50 years		
	F-M (N=174) (%, IQR)	OGC (N=667) (%, IQR)	P value	F-M (N=89) (%, IQR)	OGC (N=334) (%, IQR)	P value	F-M (N=81) (%, IQR)	OGC (N=323) (%, IQR)	P value	F-M (N=46) (%, IQR)	OGC (N=182) (%, IQR)	P value
Median age (year)	50 (18–74)	50 (19–72)	0.68	53 (19–71)	51 (18–74)	0.547	48 (19–79)	48 (18–70)	0.329	35 (19–50)	36 (18–50)	0.96
Age>60	33 (19)	111 (16.6)	0.498	15 (16.9)	64 (19.2)	0.76	18 (22.2)	43 (13.3)	0.056	0	0	
Diagnosis **AML** **MDS/AML** **MPN/AML**	134 (77) 29 (16.7) 11 (6.3)	561 (84.1) 96 (14.4) 10 (1.5)	0.002	74 (83.1) 14 (15.7) 1 (1.1)	282 (84.4) 49 (14.7) 3 (0.9)	0.941	59 (72.8) 14 (17.3) 8 (9.9)	271 (83.9) 45 (13.9) 7 (2.2)	0.004	40 (87) 5 (10.9) 1 (2.2)	169 (92.9) 12 (6.6) 1 (0.5)	0.234
Secondary AML	40 (22.9)	106 (16.4)	0.018	17 (19.2)	52 (15.6)	0.125	21 (25.9)	52 (16.1)	0.105	6 (13)	13 (7)	0.356
MRC Cytogenetic risk **Good** **Intermediate** **High**	8 (4.6) 97 (55.7) 61 (35.1)	43 (6.4) 366 (54.9) 237 (35.5)	0.652	1 (1.1) 51 (57.3) 35 (39.3)	11 (3.3) 186 (55.7) 133 (39.8)	0.592	6 (7.4) 44 (54.3) 25 (30.9)	31 (9.6) 173 (53.6) 102 (31.6)	0.822	3 (6.5) 28 (60.9) 13 (28.3)	22 (12.1) 94 (51.6) 53 (29.1)	0.64
ELN classification **Favorable** **Intermediate-I** **Intermediate-II** **Adverse**	14 (10.7) 23 (17.6) 39 (29.8) 55 (42)	65 (13.3) 83 (16.9) 145 (29.6) 197 (40.2)	0.9	4 (5.5) 17 (23.3) 19 (26) 33 (45.2)	24 (8.9) 55 (20.3) 80 (29.5) 112 (41.3)	0.716	9 (16.4) 6 (10.9) 19 (34.5) 21 (38.2)	40 (19) 25 (11.8) 63 (29.9) 83 (39.3)	0.927)	6 (20) 5 (16.7) 8 (26.7) 11 (36.7)	26 (23.9) 12 (11) 27 (24.8) 44 (40.4)	0.818
Treatment prior HSCT **>1 cycle of chemotherapy** **Prior AlloHSCT** **Prior ASCT**	173 (99.4) 6 (3.4) 2 (1.1)	660 (99) 15 (2.4) 6 (0.7)	0.776 0.619 0.428	18 (20.2) 1 (1.1) 1 (1.1)	109 (25.8) 3 (0.9) 2 (0.6)	0.789 1.0 0.509	80 (98.8) 5 (6.2) 1 (1.2)	318 (97.8) 13 (4.0) 3 (0.0)	0.495 1.0 0.376	45 (97.8) 3 (6.5) 0	180 (98.9) 6 (3.3) 0	0.413 0.39
Response prior HSCT **CR1** **CR2** **CR3+** **Active disease**	89 (51.1) 28 (16) 4 (2.3) 53 (30.4)	334 (50) 101 (15.1) 5 (0.8) 227 (34)	0.479	89 (100) 0 0 0	334 (100) 0 0 0	1.0	0 24 (29.6) 3 (4.9) 53 (31.2)	0 101 (31.3) 5 (1.5) 207 (33.1)	0.322	0 19 (41.3) 4 (8.7) 23 (50)	0 61 (33.5) 4 (2.2) 117 (64.3)	0.075
RIC	10 (5.7)	43 (6.4)	0.862	3 (3.4)	16 (4.8)	0.775	7 (8.6)	25 (7.7)	0.818	0	8 (4.4)	0.364
Stem cell source **Peripheral blood** **Marrow**	130 (74.7) 44 (25.3)	424 (63.6) 243 (36.4)	0.055	72 (80.9) 17 (19.1)	219 (65.6) 115 (34.4)	0.007	54 (66.7) 27 (33.3)	199 (61.6) 124 (38.4)	0.442	28 (60.9) 18 (39.1)	114 (62.6) 68 (37.4)	0.866
Donor **MRD** **MUD**	114 (65.5) 60 (34.5)	339 (50.8) 328 (49.2)	0.101	62 (69.7) 27 (30.3)	168 (50.3) 166 (49.7)	0.001	49 (60.5) 32 (39.5)	168 (52) 155 (48)	0.213	26 (56.5) 20 (43.5)	108 (59.3) 74 (40.7)	0.74
Engraftment	167 (96)	651 (97.6)	0.397	85 (95.5)	326 (97.6)	0.166	79 (97.5)	315 (97.5)	0.738	46 (100)	179 (98.4)	1.0

Outcomes (%)	All patients			1st CR			Beyond 1st CR			Beyond 1st CR, <50 years		
	F-M (N=174) (%, IQR)	OGC (N=667) (%, IQR)	P value	F-M (N=89) (%, IQR)	OGC (N=334) (%, IQR)	P value	F-M (N=81) (%, IQR)	OGC (N=323) (%, IQR)	P value	F-M (N=46) (%, IQR)	OGC (N=182) (%, IQR)	P value
Median time to ANC/ Platelet engraftment (day)	12/13	12/13	1.0	12/13	12/14	0.94	12/13	12/13	1.0	12/14	12/14	1.0
Day30 donor chimerism **Donor** **Mixed** **Autologous**	92 (55.1) 72 (43.1) 0	361 (55.7) 208 (41.1) 1 (0.2)	0.957	42 (48.8) 44 (51.2) 0	166 (50.5) 155 (47.1) 0	0.370	49 (62.8) 26 (33.3) 0	191 (61.8) 107 (34.6) 1 (0.3)	0.713	33 (76.7) 9 (20.9) 0	113 (66.5) 48 (28.2) 1 (0.6)	0.706
Final response **CCR/CR** **NR** **ED**	155 (92.3) 9 (5.4) 4 (2.4)	612 (92.9) 38 (5.8) 9 (1.4)	0.598	84 (97.7) 1 (1.2) 1 (1.2)	315 (95.7) 9 (2.7) 5 (1.5)	0.881	67 (85.9) 8 (10.3) 3 (3.8)	288 (90) 28 (8.8) 4 (1.2)	0.215	41 (91.1) 2 (4.4) 2 (4.4)	166 (91.7) 13 (7.2) 2 (1.1)	0.211

Abbreviations: F-M: Female donor to male recipient transplantation, OGC: other donor-recipient gender combinations, IQR: interquartile range, CR: complete remission, AML: acute myeloid leukemia, MDS/AML: acute myeloid leukemia arising from myelodysplastic syndrome, MPN/AML: acute myeloid leukemia arising from myeloproliferative neoplasm, HSCT: hematopoietic stem cell transplantation, AlloHSCT: allogeneic hematopoietic stem cell transplantation, ASCT: autologous stem cell transplantation, NR: not in remission, RIC: reduced intensity conditioning regimen, MRD: matched related donor, MUD: matched unrelated donor, CCR: complete cytogenetic remission, ED: early death

Table 2

Transplant outcomes of F-M and OGC group stratified by remission status prior to transplant

Outcomes (%)	All patients			1st CR			Beyond 1st CR			Beyond 1st 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	0.044	27.7	31.2	0.419	39.8	52	0.039	42.5	55.2	0.045
1-year NRM	23.2	15.7	0.004	17.2	13.5	0.258	29.1	17.4	0.004	35.8	25.5	0.141
Acute GVHD All grades Grade2/4 Grade3/4	51.1 28.2 10.3	50.4 28.3 5.8	0.691 1.0 0.042	48.3 16.9 4.5	48.8 27.5 3.9	0.479 0.104 0.764	54.3 39.5 16	52.3 30.2 8	0.612 0.186 0.036	52.2 32.6 17.4	46.7 25.5 7.7	0.701 0.488 0.055
Chronic GVHD All grade Extensive	44.3 34.5	37.8 26.5	0.132 0.047	50.6 37.1	41 27.5	0.418 0.09	38.3 33.3	34.7 25.4	0.284 0.162	41.3 39.1	41.2 31.1	0.266 0.38
3-year OS	43.4	44	0.449	55.3	53.7	0.706	32.8	34	0.601	32.4	40.1	0.21
3-year PFS	40.3	38.3	0.943	52.4	47.1	0.984	29.7	29.2	0.737	32.8	32.9	0.956

Abbreviations: F-M: Female donor to male recipient transplantation, OGC: other donor-recipient gender combinations, CR: complete remission, NRM: non-relapse mortality, CIR: cumulative incidence of relapse, GVHD: graft versus host disease, OS: overall survival, PFS: progression free survival

Biol Blood Marrow Transplant. Author manuscript; available in PMC 2016 April 01.

Table 3

Transplant outcomes of F-M and OGC group stratified by patient and transplant 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	42.7	40.9	0.793	43.7	48.8	0.208	34.1	41.7	0.036	20.4	11.6	0.243
<50	37.7	35.4	0.693	43.4	38.6	0.825	33.7	40.9	0.215	26.1	17.7	0.003
≥50												
Race mismatched	47.6	46.5	0.880	40	52.7	0.904	30.6	34.4	0.713	25	7.1	0.758
Yes	44.8	39.3	0.657	45.5	45.2	0.603	34.2	42	0.118	21.4	16.2	0.066
No												
Secondary AML	31	29.2	0.873	37.1	30.6	0.825	45.2	47.5	0.808	33.4	23.1	0.868
Yes	41.8	40.1	0.972	43.8	46.9	0.208	32.3	40.2	0.084	19.9	14	0.005
No												
High-risk cytogenetics	37	33.2	0.936	40.8	37.7	0.866	46.8	48.3	0.626	14.9	17.5	0.326
Yes	37.5	44.6	0.665	50	48.5	0.797	12.5	24.6	0.970	27.1	22.6	0.505
No												
ELN classification	49.8	42	0.681	55.6	52.3	0.757	23.2	26.8	0.549	25.3	27.3	0.435
Favorable	43.4	46.3	0.557	49.5	51.8	0.625	26.9	24.2	0.896	29.0	27.1	0.487
Intermediate-I	45.3	47.7	0.870	47.2	50.3	0.451	30.2	26.5	0.384	24.4	22.4	0.797
Intermediate-II	27.3	29.4	0.838	31.3	35.2	0.365	45.2	41.3	0.496	26.3	25.1	0.965
Adverse												
Active disease	29.8	19.9	0.623	21.1	24.6	0.575	50.3	60.7	0.029	37.9	18.6	0.002
Yes	52.5	47.5	0.885	55.9	53.8	0.786	25.7	32.5	0.271	16.5	14	0.201
No												
Conditioning regimens	10	21.8	0.392	20	22.8	0.495	60	58	0.816	34.4	22.3	0.376
RIC	42.2	39.4	0.823	44.9	45.5	0.519	32.3	40.2	0.045	23.7	16.6	0.006
MAC												
SC sources	43.4	37.2	0.731	42.4	43.4	0.258	32.8	40.9	0.028	25.1	14.2	0.003
Peripheral blood	31.8	40.1	0.650	46.5	44.8	0.709	37.6	41.8	0.938	21	17.6	0.421
Marrow												
HSCT types	45.5	36.7	0.230	46.2	43	0.991	37.6	42.8	0.005	22.1	14.3	0.017
MRD	30.4	40.2	0.128	38.5	45.4	0.172	46.8	39.5	0.486	25.3	16.5	0.125
MUD												

Abbreviations: F-M: Female donor to male recipient transplantation, OGC: other donor-recipient gender combinations, CR: complete remission, NRM: non-relapse mortality, CIR: cumulative incidence of relapse, GVHD: graft versus host disease, OS: overall survival, PFS: progression free survival, RIC: reduced intensity conditioning, MAC: myeloablative conditioning, MRD: matched related donor, MUD: matched unrelated donor

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	0.72	1.144	0.004	1.03	0.059	1.215	0.014
F-M	1.096	0.945	1.044	0.467	0.872	0.041	1.279	0.005
Race mismatched	1.095	0.155	1.095	0.194	0.803	0.452	1.641	0.33
Secondary AML	1.201	0.08	1.18	0.12	1.263	0.093	1.231	0.225
High-risk cytogenetics	1.124	0.201	1.12	0.243	1.405	0.004	1.485	0.195
Adverse ELN risk	1.669	<0.001	1.756	<0.001	1.342	0.031	1.1	0.842
Beyond 1st CR	1.717	<0.001	1.7	<0.001	1.348	<0.001	1.194	0.027
RIC	1.374	<0.001	1.209	<0.001	1.469	<0.001	0.741	0.339
Marrow stem cells	1.05	0.851	1.023	0.656	1.009	0.855	0.988	0.884
MUD	1.011	0.906	1.006	0.895	1.029	0.602	1.028	0.727
Mixed chimerism	1.792	<0.001	1.034	0.496	1.105	0.004	1.198	0.309
Acute GVHD	1.129	0.501	1.097	0.327	0.836	0.097	1.719	0.001
Chronic GVHD	0.333	<0.001	0.475	<0.001	0.303	<0.001	1.15	0.451

Abbreviations: F-M: Female donor to male recipient transplantation, OGC: other donor-recipient gender combinations, PFS: progression free survival, OS: overall survival, RI: relapse incidence, NRM: non-relapse mortality, RIC: reduced intensity conditioning, CR: complete remission, MUD: matched unrelated donor, GVHD: graft versus host disease

Biol Blood Marrow Transplant. Author manuscript; available in PMC 2016 April 01.

Table 5

Multivariate analyses for PFS, OS, RI, and NRM

Factor	HR	95%CI	P value
Prognostic factors for PFS			
Beyond 1st CR	0.45	0.38–0.69	<0.001
RIC	1.97	1.31–2.84	0.001
Mixed chimerism	1.13	0.94–1.62	0.135
Chronic GVHD	0.64	0.41–0.84	<0.001
Adverse ELN risk	1.71	1.37–2.13	<0.001
Prognostic factors for OS			
Age	1.01	0.91–1.22	0.331
Beyond 1st CR	0.57	0.46–0.81	<0.001
RIC	2.14	1.39–2.99	<0.001
Chronic GVHD	0.55	0.38–0.79	0.002
Adverse ELN risk	1.82	1.32–2.43	<0.001
Prognostic factors for CIR			
F-M	0.71	0.47–0.91	0.04
High risk cytogenetics	1.40	1.08–1.81	0.01
RIC	1.92	1.25–2.95	0.003
Beyond 1st CR	2.48	1.35–2.68	<0.001
Mixed chimerism	1.17	1.03–1.33	0.015
Chronic GVHD	0.52	0.35–0.77	0.001
Adverse ELN risk	1.27	1.11–1.45	0.045
Prognostic factors for NRM			
F-M	1.28	1.02–1.61	0.031
Age	1.45	1.01–2.11	0.048
Acute GVHD	1.65	1.18–2.30	<0.001
Beyond 1st CR	1.24	1.05–1.46	0.009

Abbreviation: F-M: female donor-male recipient gender combination, PFS: progression free survival, OS: overall survival, RI relapse incidence, NRM: non-relapse mortality, RIC: reduced intensity conditioning, CR: complete remission, GVHD: graft versus host disease