Impact of Donor and Recipient Sex on Outcomes of HLA-Identical Sibling Allogeneic Hematopoietic Stem Cell Transplantation.

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Abstract

Background: hematopoietic cell transplantation (HCT) is well established as therapy for hematologic malignancies as well as many non-malignant disorders. Donor selection is an important way to decrease the risks after HSCS and is therefore a key component of the clinical practice of transplantation. There are many criteria proved or hypothesized to affect outcomes after SCT and one of these, sex is the most controversial. Some investigators have found an increased risk of acute or chronic graft-versus-host disease (GVHD) associated with donor sex. Transplantation of stem cells from a female donor to a male recipient is a special circumstance in which donor T cells specific for minor H antigens, encoded by genes on the recipient Y-chromosome that are polymorphic to their X-chromosome homologues, may make a contribution to GVHD and GVL activity.**Objective:** investigate the effect of donor and recipient sex mismatch on outcomes of HLA-identical sibling allogeneic stem cell transplantation.**Methods:** this study was carried on 82 patients selected from patients who had underwent a myelo-ablative preparative regimen for a hematologic malignancy and received HSC transplant from an HLA-identical sibling being divided into 2 groups: 1st one with a female donor to a male recipient and 2nd one include otherwise. Both groups will be subjected to HLA tissue typing, CBC, Bone marrow aspirate evaluation, PT & PTT, blood culture when needed, SGPT, SGOT, ALP, blood urea, s.creatinine, urine analysis, pulmonary function tests, chest x-ray, echocardiography ECG, CMV-, EBV-, VZV-, Toxoplasma- antibodies (IgG , IgM), HBs-Ag, HBs-Ab, and HCV-Ab.**Results:** after variables controlling for patient and donor, there was an increased risk of acute GVHD in patients who received grafts from female donor being 18% for patients receiving grafts from female compared with 8% for recipients of male grafts. Donor sex was also an important influence on risk of developing chronic GVHD with cumulative incidences of chronic GVHD 9.7% for patients receiving transplants from male donors grafts compared to 24.3% for recipients of female donor grafts.**Conclusion:** we found that male recipients of grafts from female donors had a significantly higher probability for acute and chronic GVHD than male recipients with male donors or female recipients with female donors and despite the beneficial GVL effect observed in male recipients with female donors, these patients had significantly reduced survival compared with all patient/donor sex combinations, suggesting that other variables, particularly GVHD, contribute to transplantation-related mortality.

Key words: Hematopoietic cell transplantation, sex incompatibility, Graft versus host disease, Graft versus leukemia, donor sex.

Introduction

Hematopoietic cell transplantation (HCT) is well established as therapy for hematologic malignancies as well as many non-malignant disorders. Over the last several years, the spectrum of diseases that may be treated with HCT has dramatically expanded, increasing the importance of this therapeutic modality and extending HCT beyond the traditional bounds of hematology and oncology. HCT is founded on the principle that hematopoietic stem cells (HSCs) when infused, will home to and engraftin the stem cell niche within the bone marrow micro-environment, and will then proliferate
and differentiate to repopulate all lineages of the blood.[1]

Donor selection is an important way to decrease the risks after HSCS and is therefore a key component of the clinical practice of transplantation.[2] In general, HLA-identical siblings are the preferred donors, but some patients have more than one HLA-matched sibling. Thus, it is important to understand the

DOI: 10.12816/0009357

contribution of donor factors other than HLA matching to outcomes after SCT.[3]

Many criteria are known to affect outcomes after SCT and one of these, sex is the most controversial.[4] Some investigators have found an increased risk of acute or chronic graft-versus-host disease (GVHD) associated with donor sex although it is uncertain whether this risk applies just to male recipients or to all patients.[5]

Transplantation of stem cells from a female donor to a male recipient is a special circumstance in which donor T cells specific for minor H antigens, encoded by genes on the recipient Y-chromosome that are polymorphic to their X-chromosome homologues, may make a contribution to GVHD, GVL activity and graft faliure.[5]

The role of previous pregnancies in recipients of allogeneic SCT has never been evaluated, although this also has the potential to influence outcomes and may interact with donor parity.[6]

Aim of the work:

The current study aimed to study the effect of female donor to male patient on the outcome of allogeneic matched related stem cell transplantation.

Subjects and Methods:

Study design:

This retrospective study included data from 82 patients (males and females). They were selected from patients who had underwent a myelo-ablative preparative regimen for a hematologic malignancy and received HSC transplant from an HLA-identical sibling. Data were collected from files of patients who received allogeneic SCT in internal medicine department-Hematology & Stem Cell Transplantation unit in Ain-Shams faculty of medicine, Ain-Shams university, Cairo, Egypt over 2 years period. Patients were divided into 2 groups: Group A (n=38 patients): a female donor to a male recipient (F→M) and Group B (n=44 patients) included other donors and recepients (M→F), (F→F), (M→M).

Exclusion Criteria:

Allogeneic matched unrelated donor (MUD) and mismatched donors.

All participants underwent Pre-transplant and post-transplant evaluation including:

HLA tissue typing, complete blood picture, Bone marrow aspirate evaluation, Prothrombin time (PT), Partial thrompoplastine time (PTT) , blood culture when needed, liver enzymes tests (SGPT, SGOT, ALP), blood urea, serum creatinine, urine analysis, pulmonary function tests, chest x-ray, echocardiography, ECG, CMV-antibodies (IgG , IgM), EBV-antibodies (IgG, IgM), VZV-antibodies, HBs-Ag, HBs-Ab, HCV-Ab and Toxoplasma-antibodies (IgG , IgM).

Statistical analysis:

The primary study end point was GVHD. The incidence of acute GVHD was evaluated in all engrafted patients, whereas the incidence of chronic GVHD was evaluated in engrafted patients surviving for >100 days.

All data were analyzed using software (version 11, SPSS Inc., Chicago, Illinois). Baseline characteristics are presented as mean ± standard deviation for the continuous variables, and as frequency and percentage for the discrete ones. Comparisons between groups were conducted using the ANOVA. Correlation between variables was examined using the Pearson's correlation coefficient. P value < 0.05 was considered statistically significant.

Results:

The current study included 82 patients divided into two groups. Group-I included 38 male patients, the mean age was 33 (range 1-72) who were eligible for HSCT and received SCT from female donors. The diagnosis was ALL (n =16), AML (n= 13), aplastic anemia (AA) (n=5) , CML (n=3) and NHL (n=1).Group-II (n = 44) 31 Female and 13 Male patients, and include patients as follow: 9 F patients /M donor, 22 M patients /F donor and 13 M patients / M donor) with mean age of 32 (1-68), 32 (1-70) and 32 (1-72) respectively. Their diagnosis was AML (n=21), ALL (n = 9), AA (n = 9) CML (n = 4) and NHL (n =1). Other patients characteristics are shown in Table-1.

Engraftment:

Patients in group-I had statistically significant platelet engraftment at day +15 (D +15) (41.695 ± 43.589 x109 /dl) as compared to patients in group-II (25.373 ± 31.398x109 /dl) p= 0.05), while there was non-significant difference regarding neutrophils engraftment.

Graft versus host:

After controlling for patient and donor age, GVHD prophylaxis regimen, conditioning regimen and patient/donor CMV sero-status, there was an increased risk of acute GVHD in patients who received grafts from female donor. Cumulative incidence of acute GVHD at 100 days was 18% for patients receiving grafts from female compared with 8% for recipients of male grafts (table-2).

Donor sex was also an important influence on risk of developing chronic GVHD. Compared with male donors, female donors constituted risk of chronic GVHD (P= 0.06). Cumulative incidences of chronic GVHD were 9.7% for patients receiving transplants from male donors grafts compared to 24.3% for recipients of female donor grafts (table-3).

Survival analysis:

When overall survival was analyzed, female recipients had higher unadjusted survival rates compared with male recipients. After adjusting for the same variables as before, the reduced survival in male recipients was largely confined to the F→M group. Male recipients with female donors had a statistically significant higher risk for death than that for recipients in other donor/recipient sex categories (M→M, F→F and M→F).

Table 1: Donor and Patient characteristics.
(F: female, M: male, P: patient, D: donor)

	Donor/patient sex			
	Group I	Group II		
	38 F. D. To 38 M. P.	31 F. & 13 M. P. To 9 F. & 35 M. D.		
	F/M	F/F	M/F	M/M
No.	38	9	22	13
Median patient age, y (range)	33 (1-72)	32 (1-64)	32 (1-68)	33 (1-68)
Median donor age, y (range)	33 (1-78)	32 (1-68)	32 (1-70)	32 (1-72)
Disease				
AML	13	6	8	7
ALL	16	ZERO	7	2
A.A.	5	2	4	3
CML	3	1	2	1
NHL	1	ZERO	1	ZERO
Patient CMV serostatus				
Positive	37	8	21	12
Negative	1	1	1	ZERO
Donor CMV serostatus				
Positive	36	9	20	12
Negative	2	ZERO	2	1
GVHD prophylaxis				
CSP/MTX/MMF	38	9	22	13

Table 2: Cumulative incidence of Acute GVHD by donor/ patient sex.
(F: female, M: male, P: patient, D: donor)

		Acute GVHD							
		No		Yes		Total		Chi-square	
		N	%	N	%	N	%	X^2	P-value
P. sex	**F**	22	26.83	9	10.98	31	37.80	51.12	<0.001*
	M	38	46.34	13	15.85	51	62.20		
D. sex	**F**	32	39.02	15	**18.29**	47	57.32	42.451	<0.001*
	M	28	34.15	7	**8.54**	35	42.68		

Table 3: Cumulative incidence of Chronic GVHD by donor/ patient sex.
(F: female, M: male, P: patient, D: donor)

		Chronic GVHD							
		No		Yes		Total		Chi-square	
		N	%	N	%	N	%	X^2	P-value
P. sex	F	22	26.83	9	10.98	31	37.80	58.31	<0.001*
	M	32	39.02	19	23.17	51	62.20		
D. sex	F	27	32.93	20	**24.39**	47	57.32	46.1	<0.001*
	M	27	32.93	8	**9.76**	35	42.68		

Discussion

Hematopoietic stem cell transplantation (HSCT) is considered the corner stone in the treatment of haematological, and some non hematological malignancies beside some other non-malignant disorders, being a curative option of treatment.[7] Transplantation of stem cells from a female donor to a male recipient is a special circumstance in which donor T cells specific for minor H antigens, encoded by genes on the recipient Y chromosome that are polymorphic to their X chromosome homologues, may make a contribution to GVHD and GVL activity. Four genes on the Y chromosome have already been identified to encode minor H antigens, and the role of these antigens in GVHD and GVL responses is being investigated.

Donor T cells play a crucial role in the anti-leukemic activity of allogeneic HSCT, but they are also responsible for the development of GVHD.[8] There is substantial interest in identifying the molecular nature of minor H antigens that are targets of GVL responses and GVHD because this may assist in developing strategies for improving the efficacy of transplantation.

The incidence of acute graft-versus-host disease (GVHD) ranges from 10% to 90%, the mortality rate in advanced graft-versus-host disease can be disastrous.[9] As deleterious effects of acute graft-versus-host disease can involve almost all organs, including the liver, the gut, the skin and the lungs, so patients with co-morbidities other than the hematological malignancies will be more affected and can translate into a worse outcome.[10] Prior studies that have analyzed transplantation outcomes in relation to the sex of the recipients and donors found that male recipients of transplants from

female HSC donors had an increased risk for acute and chronic GVHD. The finding that female donors confer a risk of chronic GVHD may reflect the development after transplantation of cytotoxic T cells reactive against H-Y antigens, several of which have been identified as T-cell targets.[11, 12]

Anti–H-Y allo-immunization could also be mediated by antibodies. Antibodies to Y-encoded peptides have been detected in male recipients of female stem cells after transplantation in addition to normal women (pregnancy status unknown) who harbor antibodies to H-Y antigens.[13] Despite the beneficial GVL effect observed in male recipients with female donors, these patients had significantly reduced survival compared with all patient/donor sex combinations, suggesting that other variables, particularly GVHD, contribute to transplantation-related mortality.

In comparison to Randolph, et al., (2004) whose retrospective analysis was performed on data from 3238 patients who underwent a myelo-abltive preparative regimen for a hematologic malignancy and who received an unmanipulated HSC transplant from an HLA-identical sibling between 1969 and 2001 at the Fred Hutchinson Cancer Research Center **(**FHCRC**).** They examined the contribution of donor/patient sex to the risk for relapse and GVHD in patients who underwent HLA-identical sibling HSCT for hematopoietic malignancies. Compared with other sex combinations, male recipients of female transplants had the lowest risk for relapse and

the greatest odds for GVHD. They found that male recipients of grafts from female donors had a significantly higher probability for acute and chronic GVHD than male recipients with male donors or female recipients with female donors. Of interest, female recipients with male donors also had a higher likelihood of GVHD, albeit lower than male recipients with female donors. This finding has been observed previously after HLA matched, related HSCT [14, 15] but it remains unexplained. It has been suggested that proteins encoded by the X chromosome may be selectively expressed in female but not in male cells and that they provide minor H antigens that could be recognized after transplantation in females with cells from male donors.[14] An alternative is that autosomal genes regulated by sex hormones could be differentially expressed in males compared with females and could encode minor H antigens. The differential expression of an autosomal gene by donor and recipient cells as a consequence of a gene deletion in the donor has recently been shown to result in the generation of a minor H antigen in humans, providing a precedent for such a mechanism.[16]

They anticipated that the increased risk for acute and chronic GVHD observed in male recipients of HSC transplants from female donors may be associated with a reduction in the risk for leukemic relapse in comparison to our study this observe couldn't be evaluated due to short duration of our study in comparison to duration of this study.

In comparison to another study **Alison, et al., (2006)** performed between 1995 and 1999, the study population which were reported to the Center for International Blood and Marrow Transplant Research **(**CIBMTR**)** and received a non–T-cell–depleted, mylo-ablative allogeneic SCT from an HLA-identical sibling, for ALL, AML & CML. They examined the effect of donor sex and parity on outcomes of HLA-identical sibling SCT.They found that parous female donors imparted an increased risk of chronic ,but not acute, GVHD in all recipients. Furthermore , all female donors (parous and nulliparous) resulted in an increased risk of chronic GVHD in male recipients. Nulliparous female recipients had more favorable overall survival and donor parity had no effect on overall survival. The parity data for our population of HSCT patients was incomplete, and we were unable to evaluate their potential contribution to GVHD.

We found that male recipients of grafts from female donors had a significantly higher probability for acute and chronic GVHD than male recipients with male donors or female recipients with female donors and despite the beneficial GVL effect observed in male recipients with female donors, these patients had significantly reduced survival compared with all patient/donor sex combinations, suggesting that other variables, particularly GVHD, contribute to transplantation-related mortality.

However, these results should be interpreted with caution because this retrospective study included a relatively small number of Egyptian patients who received myelo-ablative allogeniec SCT. So until the effects sex on immune system are better understood, it is appropriate whenever possible to avoid female donors and to choose male donors for male recipients in HLA-identical related donor SCT.

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