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ORIGINAL ARTICLE

Outcomes Following Allogeneic Stem Cell Transplantation Using Non-sibling Family Donors

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Abstract For patients requiring allogeneic stem cell transplant, in the absence of a HLA-matched sibling, an extended donor search within the family may yield a suitable donor especially in societies with a high prevalence of consanguinity. We describe outcomes in transplants with non-sibling family donors, and compare outcomes with controls having a sibling donor transplant. Retrospective analysis of all matched related (non-sibling) donor transplants between 1995 and 2015. For comparison, appropriate age, sex and disease-matched patients were chosen from the sibling transplants (MSD) performed during the same time period (± 2 years). Comparison between the fully matched non-sibling donor cohort and age, sex and disease-matched sibling donor transplants showed a significant increase in complications in the family donor group (viral infections, acute GVHD and rejection). Event-free survival and overall survival were significantly lower in the non-sibling donor cohort, and HLA disparity (1–2 antigen) further worsened the adverse impact. Though there was a significantly lower event-free and overall survival at 3 years in the family donor cohort, this did not retain significance in the multivariate analysis. This data on allogeneic transplants using family donors showed higher complication rates and poorer outcomes. However in situations where financial constraints prevent access to matched unrelated donor sources, extended family searches may be fruitful in yielding a donor, and modifications in conditioning regimens and improvement in supportive care may help in improving the outcomes in family donor transplants.

Keywords Family donor · Allogeneic · Transplant · Non-sibling · Outcome

Introduction

Haematopoietic stem cell transplant (HSCT) is the only curative option for many haematological diseases, including thalassemia major, acute leukemia and bone marrow failure syndromes. Only 30% of patients will have a HLA-matched sibling donor, and for ethnic minorities, the chance of finding a HLA matched unrelated donor is much lower than for the Caucasian population [1–3].

In communities where the social custom of consanguineous marriages are common or where marriage is limited to within a small community, an extended family search may identify parents or other relatives who may be HLA identical with the patient [4–6]. Several small series have described outcomes in patients who have received allografts from HLA-matched non-sibling family donors (MFD), but these have generally been part of a larger cohort of alternative donors [7, 8]. Siblings or relatives may also be identified, with 1 or 2 antigen mismatches and such transplants have been as successful as fully matched transplants for certain groups of patients as matched transplants, though with an increased risk of engraftment failure [9].

This series describes outcomes in patients who have a matched family donor (MFD), and we have compared outcomes with a matched cohort of patients who received transplants from HLA identical siblings (MSD) during the same time period.

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Patients and Methods

Methodology

This is an analysis of all patients who underwent HSCT at our center using a matched (non-sibling) family donor (MFD), between 1995 and 2015. Sex and disease matched patients who were closest in age (± 2 years) and who received grafts from their HLA identical siblings (6/6 or 8/8 matched) during the same time period (± 2 years) were identified from our transplant database for comparison. If more than one appropriate sibling-donor patient was identified, the closer match (age-match given priority over transplant time period) was chosen as control.

Data on patient and donor demographics including diagnosis, degree of HLA match, CMV serostatus, and transplantation details including conditioning regimen, graft versus host disease (GVHD) prophylaxis, stem cell dose, neutrophil and platelet engraftment, infections, incidence of acute and chronic GVHD, relapse and mortality were retrieved from individual hospital records. In all sibling transplants, HLA matching was confined to HLA-A, -B, DR, and in family donor transplants subsequent to 2012, 10-antigen HLA testing (HLA,B, C DR, DQ) was done on all family donors. All patients were censored at the date of last follow-up, and data was frozen as on February 28th 2016.

Statistical Analysis

Descriptive statistics were used for all variables. A comparison between quantitative parameters was performed using a Mann–Whitney or a *t* test as appropriate, while differences in the qualitative parameters were compared using the Chi square or Fisher exact test.

Cox models were used to assess the proportional hazards for outcomes in relation to the clinically related variables including recipient/donor age, sex, degree of HLA match, complications like veno-occlusive disease, pneumonitis, infections and graft-versus-host disease. To confirm outcomes and to adjust for potential confounding factors, multivariate Cox proportional hazards models were also performed. The overall survival (OS) and event-free survival (EFS) of the family donor cohort was compared with the sibling donor cohort using a Kaplan–Meier graph and log rank (Mantel–Cox) test. EFS was calculated as survival in the absence of death, graft rejection or relapse.

For all tests a 2-sided p value ≤ 0.05 was considered statistically significant. All statistical analysis was performed using SPSS software, version 16.0 (SPSS, Chicago, IL).

Results

A total of 1496 matched related donor transplants were performed at Christian Medical College during this time period, out of which 115 (7.6%) family donor transplants were performed in 108 patients (a second transplant was done in 7). Of these, 81 were fully matched (6/6 or 10/10) family donors (MFD) and 34 transplants were performed using family donors with up to 2 antigen mismatches (MMFD).

Appropriate age, sex and disease-matched patients (n = 111) were chosen from the sibling transplants (MSD) performed during the same time period (± 2 years).

Baseline characteristics (Table 1) between the sibling donor group and the family donor group were comparable, except for the use of ATG, which was higher in the fully matched non-sibling donor group ($p = 0.02$), the use of peripheral blood as stem cell source ($p = 0.002$) and donor CMV serostatus ($p = 0.00$). Donor age was lower in the sibling transplant cohort [median age 12 years (1–52)] compared to the family donor cohort—with median age 36 years (17–66) in the fully matched group and 40 years (11–63) in the mismatched donor group ($p = 0.000$). Ninety-two transplants (80%) were for non-malignant diseases (thalassemia, aplastic anemia etc.) and 23 were for malignant disorders (details in Table 1).

Myelo-ablative conditioning regimes used included Cyclophosphamide and Total body irradiation (Cy/TBI), Fludarabine and Busulphan (Flu/Bu), Busulphan and Cyclophosphamide (Bu/Cy) and Thiotepa, Treosulphan and Fludarabine (Thio/Treo/Flu), depending on the indication for transplant, and non-myeloablative conditioning regimens included Fludarabine and Cyclophosphamide (Flu/Cy) and Fludarabine and Melphalan (Flu/Mel). There was no difference in the conditioning regimens used in the sibling donor cohort and family donor cohort ($p = 0.715$). Graft versus host disease (GVHD) prophylaxis consisted of Cyclosporine (CSA) and short course Methotrexate (MTX).

Engraftment

Unmanipulated fresh bone marrow (red cell depleted for ABO incompatible transplants) [BM] was used as graft source in 30 MFD transplants, 2 MMFD transplants and 36 MSD transplants. G-CSF stimulated peripheral blood stem cells (PBSC) was used in 50 MFD transplants, 32 MMFD transplants and 74 MSD transplants) ($p = 0.002$). One patient each in the MSD and MFD groups died prior to the scheduled transplant date. The median cell doses infused were 10×10^6 CD34 cells/kg (2.9–74.6), 10.5×10^6 (range 2.27–39.6) CD34 cells/kg and 11.4×10^6 CD34

Table 1 Baseline characteristics of all patients

	MSD (n = 111) N (%), median (range)	MFD (n = 81) N (%), median (range)	MMFD (n = 34) N (%), median (range)	*p* value
Patient age (years)	10 (1–46)	8 (1–45)	12 (1–44)	0.000
Male patient	60 (54%)	54 (69%)	16 (47%)	0.180
Donor age (years)	12 (1–52)	36 (17–66)	40 (11–63)	0.000
Male donor	55 (61%)	57 (70%)	18 (53%)	0.173
Donor	Brother 50 (45)	Father 40 (49)	Father 18 (53)	0.000
	Sister 61 (55)	Mother 28 (35)	Mother 13 (38)	
		Grandmother 7 (9)	Daughter 1 (3)	
		Cousin 4 (5)	Cousin 1 (3)	
		Uncle 1 (1)	Uncle 1 (3)	
		Nephew 1 (1)		
Pretransplant CMV serostatus				
D+/R+	47 (79.6)	27 (100)	19 (100)	$p = 0.000$
D+/R−	3 (5.1)	0 (0)	0 (0)	
D−/R+	9 (15.3)	0 (0)	0 (0)	
D−/R−	0 (0) [*n = 59]	0 (0) [*n = 27]	0 (0) [*n = 19]	
Non-malignant				
Thalassemia	49 (44.1)	36 (44.4)	14 (41.1)	
AA/FA/DKC	29 (26.1)	24 (29.6)	9 (26.4)	
PNH/OP/WAS	6 (5.4)	6 (7.4)	3 (8.8)	
Malignant				
AML	9 (8.1)	7 (8.6)	3 (8.8)	
ALL	11 (9.9)	4 (4.9)	3 (8.8)	
CML	3 (2.7)	1 (1.2)	1 (2.9)	
MDS	3 (2.7)	3 (3.7)	1 (2.9)	
Conditioning MAC				
Bu/CY	34 (30)	26 (32)	5 (15)	0.715
Treo/Thio/Flu	24 (21)	17 (21)	11 (32)	
Flu/BU	7 (6)	6 (7)	3 (8.7)	
CY/TBI	11 (10)	7 (8.5)	3 (8.7)	
Non-MAC				
Flu/CY	26 (23)	16 (20)	9 (27)	
FLU/MEL	5 (5)	2 (3)	3 (8.7)	
OTHERS	4 (5)	7 (8.5)		
ATG given	35 (32)	41 (50)	10 (32)	0.020
PB	74	50	32	0.002
BM	36 (*n = 110)	30 (*n = 80)	2	
MNC dose ($\times 10^8$/kg)	5.27 (1.96–33.9)	5.3 (2.04–54.06)	6.24 (1.12–16.26)	
CD34 cell dose ($\times 10^6$/kg)	11.43 (0.8–43) [*n = 79]	10.0 (2.9–74.6) [*n = 52]	10.51 (2.27–39.6) [*n = 30]	0.690
ANC > 500	15 (8–39)	14 (4–29)	14 (11–18)	0.498
Platelet > 20,000	15 (10–47)	16 (9–66)	13 (10–48)	0.305

MSD matched sibling donor, *MFD* matched family donor, *MMFD* mismatched family donor

cells/kg (range 0.8–43) in the MFD, MMFD and MSD cohorts respectively ($p = 0.74$).

A total of 14 patients died < 2 weeks following transplant, 5 each in the MFD (6.1%) and MMFD (14.7%) cohorts and 4 in the MSD (3.6%). There were 4 early rejections, 2 in the MSD cohort, and one each in the MFD and MMFD cohorts. In the patients who survived beyond 2 weeks, 56/73 (76.7%) in the matched family donor

cohort, 19/29 (65.5%) in the mismatched donor cohort and 80/91 (87.9%) in the sibling donor cohort successfully engrafted ($p = 0.04$). The median time to ANC > 500 was 15 days (range 8–39) in the MSD cohort and 14 days (range 4–29) in both the non-sibling donor cohorts ($p = 0.498$). Median time to platelet recovery (> 20,000/mm3) was 15 days (range 10–47) in the MSD cohort, 16 days (range 9–66) in the MFD cohort and 13 days (range 10–48) in the MMFD cohort ($p = 0.305$).

Post transplant complications (Tables 2, 3).

Infections

There was no significant difference in the incidence of bacterial infections ($p = 0.07$) and fungal infections ($p = 0.386$) between the MSD cohort and family donor groups. Viral infections were more common in the family donor cohort compared to the sibling donors ($p = 0.000$), even when the family donors were fully matched; $p = 0.05$.

Regimen-Related Toxicity

The incidence of veno-occlusive disease ($p = 0.868$), interstitial pneumonitis ($p = 0.359$) and haemorrhagic cystitis ($p = 0.563$) was similar in all 3 groups.

Graft-Versus-Host Disease

A significantly higher incidence of acute GVHD (all grades—$p = 0.002$, Grade III/IV $p = 0.05$) and chronic GVHD ($p = 0.04$) was seen in the family donor group, with 16 and 14% exhibiting grade III–IV GVHD in the MFD and MMFD cohorts respectively, compared to 5.3% in the MSD cohort.

Rejection

The overall rejection rate (early and late) was 9.5% (3.7% early rejection) in the MSD cohort, compared to 18.8% (1.3% early rejection) in the MFD cohort, and 24% (3.4% early rejection) in the MMFD cohort. Out of the 13 patients who rejected in the fully-matched family donor cohort, 8 were transplanted for thalassemia major, 4 for aplastic anemia/Fanconi anemia and one for PNH. There was no significant difference in rejection rates between the sibling donor and family donor group ($p = 0.08$), however rejections were significantly higher in the mis-matched family donor group ($p = 0.04$).

The 3 year event-free survival in the family donor group was significantly lower in the family donor cohort (47% in the MFD and 32% in the MMFD cohorts) compared with the MSD cohort (66%) ($p = 0.000$) (Fig. 1). The 3 year overall survival was significantly lower in the family donor cohort (54.4% in the MFD cohort and 35.9% in the MMFD cohort) compared to the MSD cohort (70.9%) ($p = 0.000$) (Fig. 2).

Between the MSD and MFD cohort, there was a significant difference in event-free ($p = 0.006$) and overall survival ($p = 0.03$), favoring the MSD. Relapse was seen in 5 out of 23 patients in the family donor group, compared to 8 out of 26 patients in the sibling donor group, and the numbers were too small to compare ($p = 0.47$).

Table 2 Post-transplant complications

	MSD (n = 111) N (%)	MFD (n = 81) N (%)	MMFD (n = 34) N (%)	*p* value
Interstitial pneumonitis	8 (7.3)	2 (2.5)	2 (5.9)	0.359
Haemorrhagic cystitis	8 (7.3)	5 (6.3)	4 (12.1)	0.563
Veno-occlusive disease	19 (17.3)	15 (19)	7 (21.2)	0.868
Bacterial infections	14 (13.1)	17 (21.2)	10 (29.4)	0.076
Fungal infections	10 (9)	12 (15)	3 (8.8)	0.386
Viral infections (CMV)	8 (7.2)	16 (20)	13 (38.2)	0.000
				*0.008
				**0.05
Hyper-acute GVHD	16 (14.5)	17 (21.5)	9 (27.3)	0.200
Acute GVHD	34(45.3)	41 (54.7)	17 (50)	*0.002
AGVHD grade III/IV	5 (5.3)	3 (16)	5 (14)	0.050
				*0.020
Chronic GVHD	23 (26.1)	22 (41.5)	9 (52.9)	0.040
				*0.060
Rejection	10 (9.5)	13 (18.8)	6 (24)	0.084
				*0.040

*MFD versus MSD, **MFD versus MMFD

Table 3 Causes of death

Cause of death	MSD (n = 34/111) N (%)	MFD (n = 36/81) N (%)	MMFD (n = 20/34) N (%)
RRT	4 (11.7)	4 (11.1)	4 (20)
Infection	7 (20.5)	7 (19.4)	8 (40)
Rejection	7 (20.5)	10 (27.7)	3 (15)
GVHD	5 (14.7)	11 (30.5)	3 (15)
Relapse	9 (26.4)	4 (11.1)	2 (10)

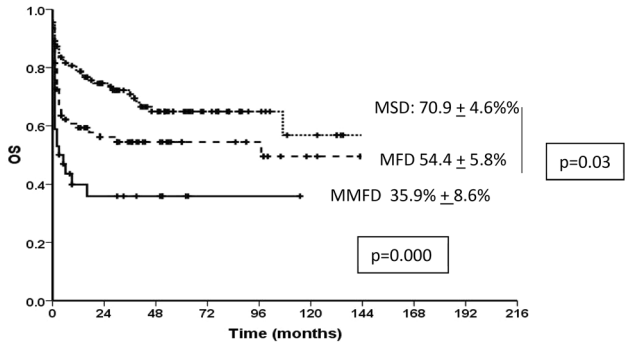

Fig. 1 Overall survival at 3 years

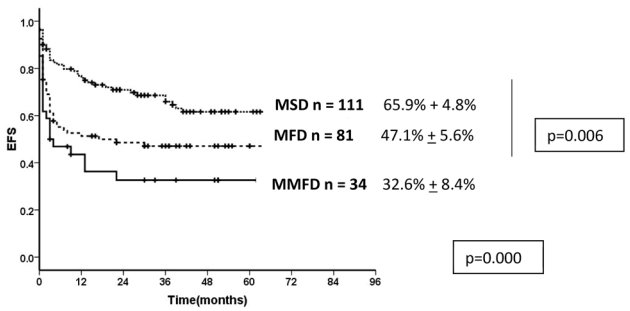

Fig. 2 Event-free survival at 3 years

Factors affecting event-free survival and overall survival are shown in Tables 4 and 5 respectively. In multivariate analysis using Cox-regression, the only variables retaining a significant impact on overall survival were patient's age, bacteremia, veno-occlusive disease, rejection and grade 3–4 acute GVHD. Only fungal infection and grade 3–4 GVHD had a significant impact on event-free survival.

Discussion

Many families conduct extended family searches to find a suitable family donor when either a suitable matched unrelated donor is not found, or when the costs of unrelated transplant are beyond the financial capability of the family. There is a paucity of data on outcomes in allogeneic stem cell transplants with this group of donors. A recent study reported a small series of 28 patients who underwent allogeneic transplant with fully matched family donors but outcomes are reports in only 7 patients [6].

In a small series from Brazil [7] describing transplant in Fanconi anemia using alternate donors as a stem cell source, 14 patients received bone marrow graft from non-sibling family donors. In this series 6/14 were single antigen (5/6) mismatches and 8/14 were 6/6 HLA matched. Outcomes were significantly worse in the 1 antigen mismatch group, with overall survival of 15%, and a high incidence of graft rejection [7]. A history of multiple transfusions (> 25) was also associated with poorer outcome and graft failure rate was 49% in the entire cohort, but is not clear whether rejection was related to the degree of mismatch.

Table 4 Factors affecting event-free survival

Univariate analysis			Multivariate analysis		
Variable	RR (95% CI)	*p* value	Variable	RR (95% CI)	*p* value
Donor type	1.9 (1.3–2.9)	0.001	Donor type	1.4 (0.8–3.1)	0.240
Patient's age	1.0 (1.0–1.03)	0.03	Patient's age	4.6 (1.0–1.04)	0.032
Donor age	1.0 (1.01–1.03)	0.000	Donor age	0.3 (1.0–1.02)	0.597
HLA match	2.0 (1.2–3.2)	0.004	HLA match	0.3 (0.6–1.2)	0.638
VOD	1.6 (1.0–2.6)	0.03	VOD	3.8 (1.0–3.0)	0.051
Bacteremia	2.0 (1.3–3.1)	0.002	Bacteremia	1.9 (0.9–2.3)	0.164
Fungal infection	3.1 (1.9–5.1)	0.000	Fungal infection	8.0 (1.3–3.9)	0.005
Acute GVHD ≥ 3	3.3 (2.0–5.5)	0.000	Acute GVHD III–IV	6.1 (1.2–3.6)	0.014
ATG	1.6 (1.0–2.5)	0.04	ATG	2.8 (0.9–2.5)	0.096

Table 5 Factors affecting overall survival

Univariate analysis			Multivariate analysis		
Variable	RR (95% CI)	*p* value	Variable	RR (95% CI)	*p* value
Donor type	1.9 (1.2–2.9)	0.003	Donor type	2.6 (0.8–5.9)	0.107
Patient's age	1.0 (1.0–1.4)	0.01	Patient's age	9.0 (1.0–1.1)	0.003
Donor age	1.2 (1.0–1.03)	0.00	Donor age	1.3 (0.9–1.1)	0.243
HLA match	2.2 (1.3–3.6)	0.001	HLA match	0.01 (0.4 –2.4)	0.919
VOD	2.0 (1.2–3.2)	0.004	VOD	4.1 (1.0–4.9)	0.043
Bacteremia	2.3 (91.5–3.7)	0.000	Bacteremia	3.9 (1.0–3.5)	0.047
Fungal infection	3.6 (2.1–6.0)	0.000	Fungal infection	1.2 (0.7–3.1)	0.261
Rejection	5.2 (2.9–9.3)	0.000	Rejection	41 (4.9–19.9)	0.000
Acute GVHD $\geq$ 3	3.8 (2.3–6.4)	0.00	Acute GVHD$\geq$ 3	21 (2.8–13.3)	0.000
ATG	1.6 (1.0–2.5)	0.03	ATG	2.6 (0.8–3.3)	0.105

Earlier reports from the EBMT group demonstrated equal outcomes between fully matched sibling and non-sibling family donors, but with a dismal survival in 1–2 antigen mismatched transplants [8]. In contrast, the Pesaro group [9] reported higher incidences of graft failure, acute and chronic GVHD in transplants from alternative family donors (mismatched siblings, mismatched and fully matched relatives). The numbers of non-sibling donors in the Pesaro cohort was small (n = 10). Harris et al. [10] also describe higher risks of rejection and GVHD even with fully matched identical relative donors, and therefore recommends use of conditioning regimens more suited to unrelated donor transplants. A larger series from Turkey describes the patterns of consanguinity in the population where up to 22% of marriages are consanguineous, and provides demographic data on 48 patients in whom the donor source was a HLA-matched family member [11]. There is no data on outcomes in these transplants.

A study from Japan [12] describes outcomes in a cohort of 135 patients with non-sibling family donors, out of which 69 were fully matched, 45 were 1–2 antigen mismatched and 21 were $\geq$ 3 antigen mismatched. Any degree of HLA mismatch was found to adversely impact outcome.

Outcomes in the non-sibling family donor group were not directly compared to sibling donors.

In contrast, a study from Iran [13] describes outcomes in 109 patients who had transplants from matched family donors, forming 20% of the total number of transplanted patients, with 2 year EFS of 71%. However, there is no direct comparison with matched sibling donors, and though event-free survival was 71%, mixed chimerism and rejection were seen in 15 and 8% respectively, with recurrence of disease in 28%. Acute (grade II–IV) and chronic GVHD rates were 33 and 20% respectively.

The current study describes 108 patients who underwent allogeneic transplant with non-sibling family donors for both malignant and non-malignant disease, and compares outcomes with between this cohort and appropriate age, sex and disease matched controls.

Comparison between the fully matched non-sibling donor cohort and age, sex and disease-matched sibling donor transplants showed a significant increase in complications in the family donor group (viral infections, acute GVHD and rejection), similar to previous reports [8–10, 12]. There were some baseline characteristics that were different (donor age, use of PBSC as stem cell source. Donor CMV seropositivity and use of ATG), and these may have contributed to the difference in outcomes. Event-free survival and overall survival were significantly lower in the non-sibling donor cohort, and HLA disparity (1–2 antigen) further worsened the adverse impact. The adverse impact of HLA-disparity in both sibling and non-sibling family donors has been noted previously, with increased rates of acute and chronic GVHD and graft rejection [12]. Though there was a significantly lower event-free and overall survival at 3 years in the family donor cohort, this did not retain significance in the multivariate analysis.

This data on allogeneic transplants using HLA-matched or partially matched non-sibling family donors showed higher complication rates and poorer outcomes. However in situations where financial constraints prevent access to the use of matched unrelated donor sources, extended family searches may be fruitful in yielding a donor, and modifications in conditioning regimens and improvement in supportive care may help in improving the outcomes in family donor transplants.

Conclusions

In societies where there is a high rate of consanguinity, an extended donor search within the family may yield a suitable donor. Complication rates appear to be higher in transplants where the stem cell donor is not a sibling, even

if fully HLA-matched, and these complications are more in the presence of a 1–2 antigen mismatch, but the donor type does not have an independent impact on event-free or overall survival.

Compliance with Ethical Standards

Conflict of interest This study was not funded and there are no conflicts of interest to disclose.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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