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OUTCOME OF UNRELATED DONOR STEM CELL TRANSPLANTATION FOR CHILDREN WITH SEVERE APLASTIC ANEMIA

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Abstract

For children with severe aplastic anemia (SAA) who fail immunosuppressive therapy and lack an HLA-matched sibling donor, unrelated donors provide a source of hematopoietic stem cells. Data from 195 children with acquired SAA who underwent unrelated donor transplantation from 1989-2003 were analyzed. Neutrophil recovery (86% at day-28) was higher with TBI-containing conditioning regimen and in younger recipients (aged ≤16 years) receiving grafts from older donors (aged >40 years). Recovery was lower after mismatched transplants and transplantations prior to 1997. Mortality rates were higher after mismatched transplants, in recipients with a poor performance score, and when the interval between diagnosis and transplantation was longer than 4 years. When restricted to donor-recipient pairs with allele-level HLA typing (8-loci; N=118), mortality rates were also higher after mismatched transplants and older recipient receiving grafts from older donors; 5-year probabilities of overall survival after HLA A, B, C, DRB1 matched and mismatched transplants adjusted for donor and recipient age were 57% and 39%, respectively (p=0.008). The data suggest that unrelated donor transplantation is an acceptable alternative for children; early referral for transplantation and identification of an HLA-matched (allele-level) donor offers the best outcome.

Keywords

SAA; unrelated donor BMT; hematopoietic recovery and survival

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Introduction

Hematopoietic stem cell transplantation (HSCT) from an HLA-matched sibling donor is the treatment of choice for children with severe aplastic anemia (SAA) (Bunin, *et al* 1996, Storb, *et al* 1994). Reported long-term survival with hematopoietic reconstitution (for groups including children and adults) in recent series (May, *et al* 1993, Storb, *et al* 1994) is 80-90%. Since most children lack suitable related donors, they are initially treated with immunosuppressive (IS) therapy and growth factors (Camitta and Doney 1990, de Planque, *et al* 1989, Loughran and Storb 1990, Speck *et al* 1986). Reported rates of partial or complete response to IS therapy range from 51-77% (Bacigalupo, *et al* 2000, Kojima, *et al* 2000, Lawlor, *et al* 1997). Non-responding patients have poor outcomes, with fewer than 30% surviving without a subsequent transplant (Bacigalupo, *et al* 2000, Kojima, *et al* 2000). Responding patients may later have a recurrence of SAA, and all patients receiving IS therapy are at risk for developing myelodysplastic syndrome or leukemia with an estimated 10-year cumulative risk 16-20% (Kojima, *et al* 2000, Socie, *et al* 1993). Outcomes of unrelated donor transplantation for SAA have been reported in small groups of children and in some larger series of both pediatric and adult patients. We report on factors affecting outcome in 195 children receiving unrelated donor bone marrow transplants for SAA facilitated by the National Marrow Donor Program (NMDP) in the United States.

Patients and methods

Data collection

A formal affiliation of the research division of the NMDP (established in 1986) and the International Bone Marrow Transplant Registry (established in 1972) led to the establishment of the CIBMTR in 2004. The CIBMTR is a working group of over 500 voluntary transplant centers worldwide that contribute detailed patient-, disease- and, transplant-characteristics and outcome data on allogeneic transplant recipients to a Statistical Center at the Medical College of Wisconsin. Participating centers register consecutive transplantations. Detailed demographic, disease and transplant characteristics and, outcome data are collected on a representative sample of registered patients and all unrelated donor transplantations facilitated by the NMDP in the U.S. Patients are followed longitudinally. Computerized error checks, physician review of submitted data and on-site audits of participating centers ensure data quality.

Inclusion criteria

The study population consisted of 195 patients aged ≤20 years with SAA who received unrelated donor bone marrow transplants in 1989-2003 in the U.S, and facilitated by the NMDP. The diagnosis of SAA was determined by the transplant centers. The diagnostic criteria for SAA are similar to those of Camitta *et al.*, (Camitta, *et al* 1979), modified so that a marrow with < 50% cellularity and < 30% hematopoietic cells also satisfies the criteria for marrow hypoplasia (in addition to the original criteria of < 25% cellularity).

Recipients of matched and mismatched transplants were included in the analysis. HLA typing was prospectively performed at the transplant centers using low-intermediate resolution molecular typing methods for HLA-A, HLA-B and high-resolution molecular typing for HLA-DRB1. In a sub-set of patients (N=118, 61%) high-resolution molecular typing was available for HLA-A, HLA-B, HLA-C and HLA-DRB1. The matching process identified all specificities that were recognized by the World Health Organization at the time of transplantation.

The NMDP retrospectively obtained consent for data submission and study participation from surviving patients or their parent/legal guardian for transplants it facilitated in the U.S.

However, the Institutional Review Board of the NMDP waived consent for patients who had died prior to soliciting consent. To overcome the inclusion of all deceased recipients, and hence their over-representation, a sample of these patients was selected using a weighted randomized scheme that adjusts for over-representation of patients who died among those consented (Farag, *et al* 2006). Thus 232 patients met the eligibility criteria and the study population includes 195 patients. Sixty-one patients (31%) in this report were included in a previously published analysis (Deeg, *et al* 1999) of 141 patients undergoing unrelated donor transplantation for SAA. Patients with Fanconi anemia or another known congenital bone marrow failure syndrome were excluded.

Endpoints

The primary outcomes studied were neutrophil recovery, acute and chronic graft-versus-host disease (GVHD) and overall mortality. Neutrophil recovery was defined as achieving an absolute neutrophil count (ANC) of $\geq 0.5 \times 10^9$/L. Failure to achieve an ANC of $\geq\geq 0.5 \times 10^9$/L or a decline to $<0.5 \times 10^9$/L after an initial recovery without a subsequent recovery was considered a graft failure. Incidence of grades 2, 3 and 4 acute GVHD and chronic GVHD were determined in all patients. Diagnosis of acute and chronic GVHD (Glucksberg, *et al* 1974, Przepiorka, *et al* 1995) was based on local institutional criteria, with overall grade of acute GVHD assigned retrospectively by the NMDP based on stage of involvement reported for each individual organ.

Statistical Analysis

The probability of overall survival was calculated with the use of the Kaplan-Meier estimator (Klein and Moeschberger, 2003). For analysis of survival, death from any cause was considered an event and data on patients alive at last follow-up were censored. The probabilities of neutrophil and platelet recovery, and acute and chronic GVHD were calculated with the use of the cumulative-incidence-function method (Klein and Moeschberger, 2003). For neutrophil and platelet recovery and GVHD, death without an event (hematopoietic recovery or GVHD) was the competing event. Data on patients without an event were censored at last follow-up. Confidence intervals were calculated with the use of a log-transformation.

Cox regression models were built for analysis of risk factors for GVHD and overall mortality and logistic regression model was built for analysis of neutrophil recovery and day-100 mortality (Cox 1972, Klein and Moeschberger, 2003). Multivariate models were built with the use of stepwise forward selection, with a p-value of 0.05 or less considered to indicate statistical significance. All variables met the proportional-hazards assumptions. Variables considered in multi-variate model building are shown in Table 1. Martingale residual plots were constructed for the following variables: time from diagnosis to HSCT, recipient and donor age to determine the appropriate donor and recipient age and interval from diagnosis to HSCT for which there were significant differences for transplant outcomes. There was a first order interaction between recipient and donor age and this interaction term was held in all steps of model building. P-values are two-sided. Analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC).

Results

Patients

Patient-, disease- and transplant characteristics are shown in Table 1. Median time from diagnosis to HSCT was 13 months and the median age at transplantation, 10 years. Twenty percent of patients had poor performance score (<90) and 40% had received over 50 red blood cell transfusions prior to transplantation. All patients received bone marrow grafts;

27% were T-cell depleted. Most (76%) patients received total body irradiation (TBI) containing conditioning regimens. Sixty-six percent of transplants were matched at HLA A and B by low or intermediate resolution and DRB1. High resolution typing at HLA-A, HLA-B and HLA-C were available for 118 of 195 (61%) patients. Of these, 48 (41%) were matched and the remaining 70 (59%) were mismatched at ≥1-loci. The median follow-up of surviving patients was 59 months (range 6-162).

Neutrophil recovery

One hundred and seventy eight patients achieved neutrophil recovery; median time to recovery was 18 (range 7-56) days. Seventeen patients failed to achieve neutrophil recovery. The probabilities of neutrophil recovery at days 28 and 100 were 86% (95% CI 75-92)% and 91% (95% CI 77-97), respectively. Seventeen patients failed to achieve neutrophil recovery. Among the 178 who achieved neutrophil recovery, 15 subsequently experienced a sustained decline in their neutrophil count. The probabilities of graft failure at 28 days and 1-year were 10% (95% CI 6-15 and 15% (95% CI 11-21), respectively. One hundred and twenty-three of 176 patients achieved platelet recovery; median time to recovery was 28 (range 9-267) days. The day-60 and day-100 probabilities of recovery were 59% (95% CI 50-66) and 63% (95% CI 54-71), respectively.

The probability of neutrophil recovery at day 28 was significantly after an irradiation-containing conditioning regimen and younger patients (aged ≤16 years) who received grafts from donors older than 40 years (Table 2). The probability of recovery was lower in recipients of intermediate-resolution mismatched transplants (defined as any mismatch at the antigen level for HLA-A or B, or any allele-level mismatch at DRB1) and transplants performed prior to 1997. When restricted to donor-recipient pairs with allele-level typing at Class 1 and 2 (n=118), the probability of recovery was also higher after an irradiation containing regimen: odds ratio (OR) 7.85, p=0.02 and OR 6.69, p=0.01 after TBI ≤600 cGy and ≤1000 cGy, respectively. Recovery was lower after mismatched transplants (defined as any allele-level mismatch at HLA-A, B, C or DRB1; OR 0.18, p=0.01).

Acute and chronic GVHD

Grade 2-4 acute GVHD occurred in 84 patients. The day-100 probability of acute GVHD was 43% (95% CI 36-51). Grade 2-4 acute GVHD rates were lower in recipients of T-cell depleted grafts (relative risk [RR] 0.30, p=0.001) and higher in patients with poor performance scores (RR 1.75, p=0.026). A similar trend was observed in subset analysis restricted to the 118 patients with allele-level HLA typing at 8-loci (t-cell depleted grafts: RR 0.44, p=0.027; poor performance scores: RR 2.29, p=0.017). We did not observe an effect of HLA disparity (low/intermediate or allele-level typing) on grade 2-4 acute GVHD.

Chronic GVHD occurred in 63 patients. The 5-year probability of chronic GVHD was 35% (95% CI 27-43). No significant risk factors were identified when we considered low/intermediate resolution at Class 1 and DRB1. However, when restricted to patients with allele-level HLA typing at Class 1 and 2 loci, chronic GVHD rates were higher after allele-level mismatched transplants (RR 2.05, p=0.03).

Overall survival

Ninety-five patients died after transplantation. Of these 60 (63%) died within 100 days after transplantation (early mortality). Early mortality rates were higher if transplants were performed after 4 years from diagnosis (OR 2.61, p=0.04), in recipients with poor performance scores (OR 3.99, p<0.001) and donors aged >40 years (OR 2.36, p0.04; OR 6.14, p=0.005; recipients aged ≤16 years and >16 years, respectively). Overall mortality rates were also higher when transplants were performed after 4 years from diagnosis, in

recipients with poor performance scores and in intermediate-resolution mismatched transplants (Table 3). The 5-year probability of overall survival was 51% (95% CI 44-58).

In subset analysis restricted to the 118 patients with allele-level typing at HLA A, B, C and DRB1, early and overall mortality rates were higher after ≥1-loci mismatched transplants, in recipients with poor performance scores and in older recipients receiving grafts from older donors (Table 4A,B). The 5-year probabilities of overall survival after HLA A, B, C, DRB1 matched and mismatched transplants adjusted for recipient and donor age were 57% and 39%, respectively (p=0.008; **Figure 1**).

Causes of early mortality included graft failure (n=21), GVHD (n=13), infection (n=10), organ toxicity (n=6), hemorrhage (n=5) and other causes (n=5). Death beyond 100 days (late mortality) occurred in 35 patients. GVHD (n=7), graft failure (n=6), infection (n=5) and adult respiratory distress syndrome (n=5) were common causes of mortality. Other causes were organ toxicity (n=4), hemorrhage (n=3), malignancy (n=2) and other causes (n=3).

Discussion

Although there are some reports describing outcomes after unrelated-donor HSCT in children with SAA, these are limited by relatively small numbers of patients and often transplanted at a single institution (or small numbers of institutions) (Gajewski, *et al* 1990, Gustafsson, *et al* 2000, Margolis, *et al* 1996). The current report focuses on 195 children and adolescents undergoing unrelated donor bone marrow transplantation facilitated by the NMDP and also examine the effect of allele-level HLA typing at HLA A, B, C and DRB1 on transplant outcome. In an earlier report from the NMDP, Deeg and colleagues examined outcomes in 141 children and adults who underwent unrelated-donor bone marrow transplantation for SAA facilitated by the NMDP between 1988 and 1995 (Deeg, *et al* 1999); 61 patients in the current report were included in that report. Overall survival rates reported by Deeg and colleagues was somewhat lower (34% at 5 years) compared to the current report (51% at 5 years). They observed higher mortality rates when transplantations occurred after 3 years from diagnosis and when donor and recipient were mismatched. The higher survival rate in the current report is excepted as this report includes more recent transplants, better donor-recipient matching based on allele-level HLA typing at 8-loci and limited to patients aged ≤20 years.

A recent report from the Japan Marrow Donor Program (JMDP) examined outcomes after unrelated donor HSCT in 154 children and adults with SAA (**Kojima, *et al* 2002**). Though survival rates were not reported separately for children and adults, the 5-year overall survival rate reported by the JMDP is 56% and comparable to ours. Similar to our observations, neutrophil recovery was better after TBI-containing regimens. Acute GVHD rates were higher when donor-recipient pairs were mismatched at HLA A or B and received non anti-lymphocyte globulin (ALG) containing conditioning regimen. Chronic GVHD rates were higher in patients who had acute GVHD or an A or B locus mismatch. We were unable to show an association between HLA mismatch and acute GVHD but consistent with the JMDP report, chronic GVHD rates were higher after mismatched transplants. Our inability to show an association between HLA disparity and acute GVHD may be attributed to the inclusion of t-cell depleted bone marrow grafts (approximately a third of transplants) and in itself a predictor for lower rates of acute GVHD (Ho and Soiffer 2001). T-cell depletion did not have an effect on hematopoietic recovery, chronic GVHD or overall survival. None of the patients in the current report received ALG. The use of anti-thymocyte globulin (ATG) in the current report was associated with the intensity of conditioning regimen such that ATG was included in the regimen for 29% of patients who received TBI ≥1000 cGy, 63% of patients who received lower dose TBI or limited field irradiation and 86% of patients who

received non-irradiation regimens received ATG. Consequently we examined the impact of the three groups (TBI ≥1000 cGy containing regimens vs. lower dose TBI/limited field irradiation vs. non-irradiation regimens) and did not observe an effect on overall survival. Neutrophil recovery was more likely after irradiation containing regimens, regardless of dose of irradiation. We were unable to examine the inclusion of fludarabine in conditioning regimens as very few patients received this drug.

Passweg and colleagues recently reported on 232 children and adults with SAA who underwent unrelated donor HSCT, and 86 additional patients who underwent HSCT from a mismatched related donor (Passweg, *et al* 2006). One-hundred sixty-eight (72%) of were less than 21 years old. Mortality rates were higher in older patients and in those with poor performance scores. Unlike the current report, Passweg and colleagues **did not** observe an effect of donor-recipient HLA disparity or time from diagnosis to transplantation on mortality. The absence of an effect of HLA disparity is not readily explained and the inclusion of mismatched related donors in their analysis may have played a role. The effect of time interval from diagnosis to transplantation is difficult to study; on the one hand earlier transplantations with fewer therapies and transfusion exposures are favorable and yet, a longer interval to transplantation may be the result of a sustained response to IS therapy and consequently fewer therapies and transfusion exposures. The higher rates of mortality observed by us and others in patients with a rather long interval from diagnosis to transplantation may be a consequence of end-organ damage from infectious or hemorrhagic complications or side effects of medications used for the treatment of SAA (e.g. cyclosporine and renal toxicity) or sensitization to blood products from repeated transfusions. It is noteworthy that when donor-recipient HLA match is considered using allele-level typing at 8-loci, HLA disparity and age of the donor and recipient (older persons) are the only factors to have a significant effect on survival.

The optimal number of courses of IS therapy to try before proceeding to unrelated donor transplantation is not clear. Data on number of courses and timing of administration of IS therapy were not collected and we were unable to examine the effect of number of courses of IS therapy on transplantation outcome. The data presented herein suggest overall survival rates after unrelated donor transplantation for children and adolescents with SAA have improved and likely secondary to availability of higher resolution HLA typing (allele-level) at HLA A, B, C and DRB1. Though we were unable to observe an effect of conditioning regimen on overall survival in the current report, data from others (Deeg, *et al* 2006) suggest the optimal conditioning regimen for patients with SAA to be low dose TBI (200 cGy), cyclophosphamide and ATG. When an allele-matched donor is available, early referral for transplantation is favored when patients fail their first course of IS therapy or experience a recurrence of SAA after initial response. Reported response rates to the first cycle of IS therapy range from 50-56%, and response rates to a second cycle of IS therapy (for patients who did not respond to the first course) range from 35-45% (Bacigalupo, *et al* 2000, Lawlor, *et al* 1997, Schrezenmeier, *et al* 1993). Since a significant number of patients respond a second cycle of IS therapy, it appears reasonable to try at least two cycles before moving to unrelated donor transplantation for older patients and those who lack an allele-matched unrelated donor.

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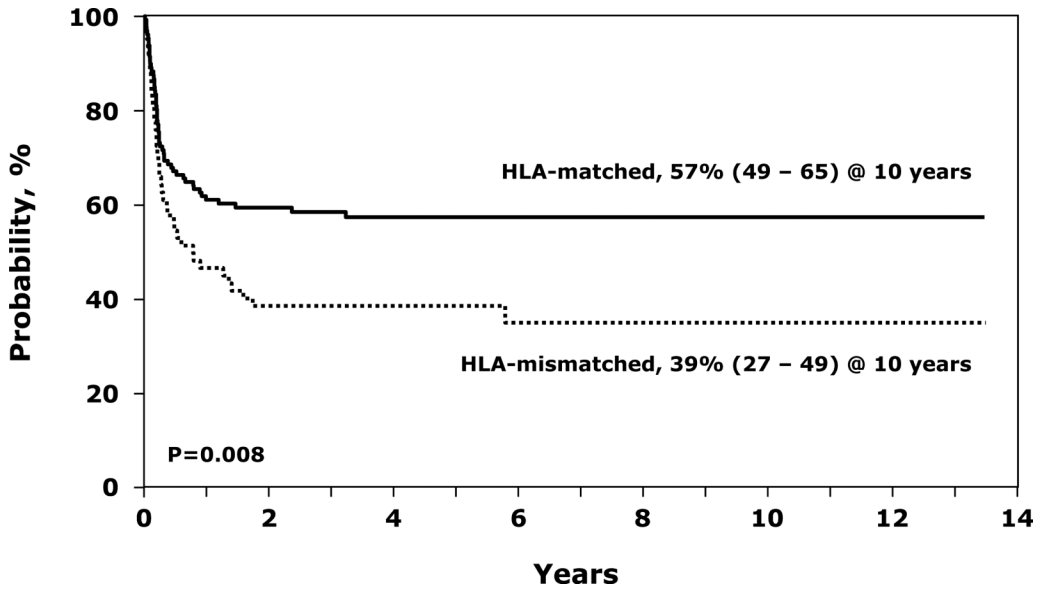

Figure 1.
The probabilities of overall survival after HLA A, B, C DRB1 allele-matched and mismatched transplants adjusted for recipient and donor age.

Table 1

Patient-, disease- and transplant characteristics.

Variable	N (%)
Number of patients	195
Male	109 (56)
Age at diagnosis, years	
< 5	51 (26)
5 – 10	64 (33)
>10 – 20	80 (41)
Etiology of aplastic anemia	
Idiopathic	159 (82)
Hepatitis	10 (5)
Drug-induced	2 (1)
Other	5 (2)
Unknown	19 (10)
Number of red blood cell transfusions prior to transplant	
None	2 (1)
1 – 20	33 (17)
21–- 50	33 (17)
> 50	78 (40)
Unknown	49 (25)
Pre-transplant treatment	
None	13 (7)
Cyclosprorine + ATG ± cytokines/steroids	128 (66)
Androgens ± other	13 (7)
Other	21 (11)
Unknown	20 (10)
Time from diagnosis to transplant, months	
≤ 6	40 (21)
>6 –12	53 (27)
>12 – 24	50 (26)
> 24 - 48	23 (12)
> 48	29 (15)
Age at transplant, years	
<5	30 (15)
5 – 10	58 (30)
>10 – 21	107 (55)
Year, transplant	
1989 – 1996	80 (41)
1997 – 2003	115 (59)
Performance score	
90 – 100	151 (77)

Variable	N (%)
> 90	39 (20)
Unknown	5 (3)
Conditioning regimen	
Radiation regimens	
TBI (≥1000 cGy) + Cy	47 (24)
TBI (≥1000 cGy) + Cy ± Ara-C/etoposide	44 (23)
TBI (≥1000 cGy) ± Ara-C/etoposide	2 (1)
TBI (510-600 cGy) + Cy ± other	17 (9)
TBI (200-400 cGy, frac) + Cy ± other	18 (9)
TBI (200-400 cGy, single) + Cy ± other	20 (10)
TLI/TAI + Cy ± other	18 (9)
Non-radiation regimens	
Cyclophosphamide (200 mg/kg) + ATG	8 (4)
Cyclophosphamide (<200 mg/kg) + ATG	7 (4)
Cyclophosphamide (200 mg/kg) + fludarabine	11 (6)
Busulfan (>9 mg/kg) + other (includes fludarabine)	3 (2)
GVHD prophylaxis	
T-cell depletion	53 (27)
Cyclosporine/methotrexate ± other	103 (53)
Cyclosporine ± other	19 (10)
Tacrolimus ± other	19 (10)
Methotrexate/steroids	1 (<1)
Donor age, years	
18 – 30	58 (30)
31 – 40	76 (39)
41 – 50	53 (27)
51 – 60	8 (4)
Donor-recipient compatibility	
Intermediate-resolution matched	129 (66)
Intermediate-resolution mismatched	66 (34)
Donor parity	
Male	109 (56)
Female (nulliparous)	66 (34)
Female (any parity)	20 (10)
Donor-recipient sex match	
Male → male	73 (37)
Male → female	47 (24)
Female → male	36 (18)
Female → female	39 (20)
Donor-recipient CMV status	
Donor (-) / Recipient (-)	59 (30)
Donor (-) / Recipient (+)	66 (34)

Variable	N (%)
Donor (+) / Recipient (-)	29 (15)
Donor (+) / Recipient (+)	38 (19)
Unknown	3 (2)
Follow-up, median (range), months	59 (6 – 162)

Abbreviations: ATG=anti-thymocyte globulin; TBI=total body irradiation; TLI=total lymphoid irradiation; TAI=total abdominal irradiation; Cy=cyclophosphamide; Ara-C=cytarabine; CMV=cytomegalovirus.

Table 2

Factors affecting the probability of neutrophil recovery at day 28 for patients with low-intermediate resolution typing at HLA A, B and high resolution typing at HLA DRB1

Variable	N	Odds ratio 95% confidence interval	P-value
Conditioning regimen			
Non-irradiation regimen	28	1.00	0.002
TBI (≥1000cGy) + other	91	8.24 (2.24 – 30.33)	0.002
TBI (≤ 600 cGy)/TLI/TAI	71	7.25 (1.97 – 26.70)	0.003
Donor-recipient HLA compatibility			
Intermediate-resolution match	126	1.00	
Intermediate-resolution mismatch	64	0.25 (0.09 – 0.70)	0.009
Donor and recipient age, years			
Donor (≤40) and recipient (≤16)	96	1.00	0.024
Donor (≤40) and recipient (>16)	34	1.43 (0.34 – 5.98)	0.625
Donor (>40) and recipient (≤16)	46	6.09 (1.16 – 31.97)	0.033
Donor (>40) and recipient (>16)	14	0.31 (0.08 – 1.21)	0.091
Year, transplant			
1997-2003	110	1.00	
1989-1996	80	0.35 (0.12 – 0.97)	0.044

Table 3

Factors affecting overall mortality for patients with low-intermediate resolution typing at HLA A, B and high resolution typing at HLA DRB1

Variable	N	Relative Risk 95% confidence interval	P-value
Performance status at transplant			
90 – 100	151	1.00	
< 90	39	2.11 (1.34 - 3.34)	0.001
Time from diagnosis to transplant			
≤ 4 years	163	1.00	
> 4 years	27	2.96 (1.77 - 4.93)	<0.001
Donor-recipient HLA compatibility			
Intermediate-resolution match	126	1.00	
Intermediate-resolution mismatch	64	1.82 (1.19 – 2.77)	0.006

Table 4A

Factors affecting early mortality rates for patients with allele-level HLA typing at HLA A, B, C and DRB1

Variable	N	Odds ratio 95% confidence interval	P-value
Performance status at transplant			
90 – 100	100	1.00	
< 90	18	5.49 (1.65 18.30)	0.006
Donor and recipient age, years			
Donor (≤40) and recipient (≤16)	50	1.00	0.006
Donor (≤40) and recipient (>16)	23	4.32 (1.22 – 15.37)	0.024
Donor (>40) and recipient (≤16)	32	4.89 (1.57 – 15.20)	0.006
Donor (>40) and recipient (>16)	13	10.93 (2.59 – 46.18)	0.001

Table 4B

Factors affecting overall mortality rates for patients with allele-level HLA typing at HLA A, B, C and DRB1

Variable	N	Relative Risk 95% confidence interval	P-value
Donor-recipient HLA compatibility			
Allele-level match	48	1.00	
Allele-level mismatch	70	2.84 (1.53 – 5.26)	0.001
Donor and recipient age, years			
Donor (≤40) and recipient (≤16)	50	1.00	0.010
Donor (≤40) and recipient (>16)	23	1.77 (0.84 – 3.74)	0.135
Donor (>40) and recipient (≤16)	32	1.85 (0.96 – 3.57)	0.067
Donor (>40) and recipient (>16)	13	3.96 (1.75 – 8.95)	0.001