Title: Recipient/Donor HLA and CMV matching in recipients of T cell depleted unrelated donor haematopoietic cell transplants

Short title: Donor factors in transplant outcome

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Recipient/Donor HLA and CMV matching in recipients of T cell depleted unrelated donor haematopoietic cell transplants

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Abstract

Improving haematopoietic cell transplantation outcomes by selection of an HLA matched unrelated donor is best practice, however donor selection by secondary characteristics is controversial. We studied 1271 recipients with haematological malignancies who underwent T cell depleted allografts and who had complete data on HLA matching status for six loci (HLA-A, -B, -C, -DRB1, -DQB1, -DPB1) and clinical outcome data. 5-year overall survival was 40.6%. HLA mismatching (at HLA-A, -B, -C, -DRB1, -DQB1) (Relative Risk (RR) 1.22, 95% CI 1.2-1.5, p=0.033 for 1 mismatch and RR 1.46, 95% CI 1.1-1.9, p=0.009 for >1 mismatch) and CMV mismatching (RR 1.37, 95% CI 1.2-1.6, p<0.001) were significantly associated with inferior survival. Donors under 30 years were associated with a trend towards better survival (RR 1.17, 95% CI 0.99-1.4, p=0.069). In a multivariate model for mortality combining CMV and HLA match status, we found a RR of 1.36 (95% CI 1.1-1.7, p=0.003) for HLA matched/CMV mismatched, a RR of 1.22 (95% CI 0.99-1.5, p=0.062) for HLA mismatched/CMV matched and a RR of 1.81 (95%

CI 1.4-2.3, p=<0.001) for HLA/ CMV mismatched, compared to the HLA/CMV matched recipients. These data suggest that HLA and CMV matching status should be considered when selecting unrelated donors and that CMV matching may abrogate the effect of an HLA mismatch.

Introduction

Haematopoietic cell transplantation (HCT) is curative for many recipients suffering from haematological and immunological disorders. Survival using unrelated donors (UD) has improved significantly over time and is now equal to that of sibling transplants in many settings.(1) A reason for this improvement is the enormous expansion in the internationally available UD pool, with over 25 million donors listed on Bone Marrow Donors Worldwide (BMDW) in 2015 (http://www.bmdw.org/accessed 20/4/2015). HLA matching for 10/10 loci is often considered the gold standard, but the importance of HLA-DQB1 matching has been questioned.(2, 3) Conversely, the additional benefit to matching for DPB1 has been increasingly studied.(4-6) In addition, studies report a differential impact of single allele mismatches on transplant outcomes.(2, 7, 8) Due to the expansion in volunteer donors numbers recipients now often have a choice between several equally HLA matched donors and in this setting secondary donor characteristics such as donor age, gender, parity, CMV serostatus and ABO type should be taken into account.(3, 9) Although these factors may currently be considered by the team making the final donor selection, no widespread

internationally agreed selection algorithms are available. Selection of these factors has changed significantly over time. CMV seronegative donors (D-) were originally chosen for all recipients. More recently a CMV seropositive donor has been preferred for a CMV positive recipient, however this remains controversial, despite some studies supporting it.(10, 11) Studies show that younger donors generally result in improved outcomes, but the impact of ABO mismatches and the use of female donors have produced conflicting results. (3, 9)

The aim of this study was to analyse the impact of HLA and non-HLA donor factors on transplant outcomes and to identify those factors important in donor selection.

Recipients, material and methods

Study population

The final study population includes 1271 UK recipients, both children and adults, transplanted for a haematological malignancy, from September 1996 to October 2011, from an UD through Anthony Nolan. 1370 paired samples that were collected pre-transplant or pre-donation for recipients and donor respectively and stored in the sample repository were successfully typed, however 99 recipients were not included in the final study population due to incomplete clinical data. Both recipient and donor were required to have two field (previously 4-digit) allele typing results at six HLA loci (HLA-A, -B, -C, -DRB1, -DQB1, -DPB1). Clinical data were collected by the Anthony Nolan Research

Institute in collaboration with the British Society for Blood and Marrow Transplantation, using standard post transplant reporting forms. Standard definitions for primary graft failure (PGF), graft versus host disease (GVHD) and non-relapse mortality (NRM) were used. Relapse was defined as clinical evidence of disease. The EBMT score was calculated based on the publication by Gratwohl *et al.*(12) CMV prophylaxis was not routinely given, instead screening and pre-emptive treatment strategies were used.

Ethical permission

The study has ethical approval from the United Kingdom's National Research Ethics Service (www.myresearchproject.org.uk, application number MREC 01/8/31). All recipients and donors signed informed consent.

Statistical Methods

Probability curves were calculated using the Kaplan-Meier method for survival and the cumulative incidence procedure for NRM and relapse. Time intervals were calculated relative to the date of transplantation, until the event of interest (or competing event), or until the date of last follow-up. Groups were compared using either the log rank test or Gray's test as appropriate. Factors found to be significant at the $P < 0.1$ level were entered into either Cox regression or Fine and Gray (13) models, using a backward stepping procedure to find the best model. Incomplete time to event data for PGF and Grade II-IV aGVHD resulted in these outcomes being described as simple proportions, with logistic regression analysis being utilised to find significant factors associated with each outcome. All analyses were performed using either SPSS version 22 software (SPSS, Inc.,

Chicago, IL) or R (14). All statistical tests were 2 sided, and $P < 0.05$ was used to indicate statistical significance.

Results

Recipient and donor factors are shown in Table 1 arranged by transplantation era. Disease for which transplantation was performed were acute leukaemia (581, 46%), myelodysplasia (221, 17%), chronic leukaemia (174, 14%), lymphoma (198, 16%), myeloma (46, 4%) and other (51, 4%). 94% of the population received T cell depletion (TCD) with Alemtuzumab. As expected, the use of myeloablative conditioning decreased over the eras with a corresponding increase in the use of Peripheral Blood Stem Cells (PBSC). Recipients were significantly older in the later eras. There was a reduction in the number of HLA mismatched donors over time. Donors were also more likely to be younger and CMV seropositive donors (D+) were more likely to be selected for CMV seropositive recipients (R+) in the later eras.

The 5yr probability of survival for the whole group was 40.6%, with NRM at 1, 3 and 5 years of 26.5%, 34.3% and 37.4% respectively. The relapse risk at 1, 3 and 5 years was 29.2 %, 39.2% and 42.1% respectively. Overall PGF rate was 3.8%. Acute GVHD was present in 28% of recipients (grade 2 in 18%, grade 3/4 in 10%).

Factors implicated in recipient survival and mortality

Results of the univariate analysis of recipient and donor factors are shown in Table 2. Older recipients (p=0.005), R+ (p=0.013), those who had a previous autograft (p=0.001) and intermediate or poor EBMT risk status (p<0.001) had a worse OS. There was a trend to a worse OS with the use of Bone Marrow (BM) compared to PBSC (p=0.078).

Recipients matched for 10/10 HLA alleles had significantly better OS and reduced NRM compared to those matched at 9/10 or <9/10 (5yr OS: 43.1 vs 35.6 vs 28.4 respectively, p=0.001 (Figure 1) and NRM at 1yr : 20.3% vs 26.0% vs 33.4% respectively, p=0.007). Considering individual locus mismatches compared to 10/10 matched recipients, mismatching for HLA-B (p=0.011) and –DQB1 (p=0.03) resulted in a significantly worse survival, while mismatching for HLA-A (p=0.17), -C (p=0.28) or -DRB1 (p=0.75) resulted in no statistically significant difference in survival (table 2).

HLA-DPB1 matching was not associated with a statistically significant survival advantage (5yr OS for 12/12 was 46.5% vs 42.5% in 10/10 matches, p=0.1). Non-permissive HLA-DPB1 T-cell Epitope (TCE) matching status was associated with a trend towards worse survival and a significantly higher NRM 5yr OS in DPB1 TCE matched, allele matched or TCE mismatched pairs was 43.0%, 41.5%, and 36.9% respectively, p=0.054) and NRM at 1 year was 19.3%, 23.6% and 26.4% respectively, p=0.028 (Table 2).

There was no impact of donor CMV on either OS or NRM as an independent variable, however a significant effect was observed for CMV matching status

between recipient and donor. Recipients who had a CMV matched donor had an OS of 44.1% vs 32.2% for those who were mismatched (p<0.001). Survival in the R+/D+ setting was 40.5% compared to 30.0% in the R+/D-. We also noted a difference in the CMV negative recipient where R-/D- had a survival of 45.3% compared to 37.9% in the R-/D+ (Table 2). NRM at 1 year was 19.1% vs 30.4% for the CMV matched vs mismatched recipients (p<0.001) (Table 2). Use of donors under the age of 30 resulted in a better survival (45.3% vs 38.6%, p=0.01) and a trend to lower NRM (19.2% vs 27.9%, p=0.075). An ABO match or minor mismatch was preferential to a major or bidirectional mismatch (OS: p=0.011and NRM: p=0.040).

In multivariate analysis (Table 3), the only recipient factor resulting in worse OS was older age. Recipients with a previous autograft and/or intermediate or poor EBMT disease risk score had a worse OS. OS and NRM were significantly worse in those who had a transplant prior to 2004 and 2000 respectively. HLA matching remained significant, as those who had >1 HLA mismatch with their donor had a Relative Risk (RR) of 1.43 (95% CI 1.1-1.9, p=0.016) for mortality and 1.59 (95% 1.1-2.4, p=0.028) for NRM. Although there remained a survival detriment when comparing a single mismatch to recipients with a 10/10 matched donor (OS: RR 1.21 (95% CI 1.1-1.5), p=0.042) there was no significant impact on NRM: RR 1.24 (95% CI 0.9-1.6), p=0.14). Recipients who were CMV mismatched with their donor had a significant survival detriment (OS: RR 1.40, 95% CI 1.2-1.6, p<0.001; NRM: RR 1.63, 95% CI 1.3-2.1, p<0.001. Use of donors >30 showed a trend towards worse OS (RR 1.17 (95% CI 0.98-1.4, p=0.078), but no impact on NRM. In contrast, recipient/donor gender matching did not impact on OS, while a female

218 donor into a male recipient showed a trend to higher NRM compared to all other
219 gender combinations (RR 1.38, 95% CI, 0.99-1.9, p=0.063). Recipient donor ABO
220 matching status and the DPB1 TCE were not significant for either OS or TRM.
221
222 **Disease Relapse**
223 Four factors were shown to be associated with an increase in disease relapse in
224 univariate analysis, including recipients of a prior autograft (5 yrs: 54.2% vs
225 40.0%, p<0.001); earlier transplant era (p=0.012); BM vs PBSC (45.2% vs 38.7%,
226 p=0.024 and the use a DPB1 TCE or allele matched donor vs a TCE mismatch
227 donor (p=0.036). CMV status of either the patient or donor, or the combinations,
228 were not associated with relapse risk. In multivariate analysis, donor CMV status
229 was the only donor factor associated with relapse (D+: RR 1.23 95% CI 1.1-1.5,
230 p=0.035), whilst prior autograft and era retained significance (Table 4).
231
232 **CMV status in the context of HLA matching**
233
234 We further examined the relationship between recipient/donor CMV and HLA
235 matching (Figure 2a). Outcomes differed significantly based on the four possible
236 combinations (p=<0.001). In the HLA matched setting, survival was significantly
237 better in those who were CMV matched (n=676) compared to CMV mismatched
238 (n=223) (5yr OS 45.9% vs 35.9%, p=0.007). Likewise, in the HLA mismatched
239 setting, CMV matched recipients (n=207) again had a better survival than those
240 who were CMV mismatched (n=122) (5yr OS 38.6% vs 25.8%, p=0.002). These
241 findings were consistent when adjusted for other significant variables in a
242 multivariate analysis (Figure 2b). When compared to the HLA matched, CMV

matched recipients: there was a RR 1.36 (95% CI 1.1-1.7, p=0.003) for HLA matched and CMV mismatched, a RR 1.22 (95% CI 0.99-1.5, p=0.062) for HLA mismatched and CMV matched, and a RR 1.81 (95% CI 1.4-2.3, p<0.001) for HLA and CMV mismatched.

Impact of donor factors on other outcomes

In multivariate analysis, a mismatch of more than one HLA allele (RR 2.9, 95% CI 1.2-7.3, p=0.02) and the use of BM (RR 2.9, 95% CI 1.2 – 7.3, p=0.02) resulted in significantly higher PGF. HLA matching (OR 0.63 95%CI 0.5-0.8, p=0.002), the use of BM (OR 0.59, 95% CI 0.4-0.8, p=0.001) and CMV seronegative donors (OR 0.65, 95% CI 0.5-0.9, p=0.006) were associated with a lower risk of grade 2-4 aGVHD (Table 4).

Discussion

Our results show that donor factors remain a critical determinant of outcome in UD HCT, despite the changing trends in transplant practice over recent eras. We found both HLA matching and the recipient/donor match status for pre-transplant CMV serostatus to be the most significant factors determining survival and report the novel finding that avoiding a CMV mismatch may offset the negative impact of an HLA mismatch. In addition, we confirmed the previous observations that HLA matching and donor age impact survival.

Although the relationship between CMV and HLA matching in this study is a novel finding, it is consistent with observations and proposed mechanisms made in several recent studies. Historically it is well recognised that recipient CMV seropositivity (R+) is associated with an inferior transplant outcome (15, 16), but studies regarding the impact of donor status have produced controversial results (3, 9, 17) and recommendations for donor selection based on this criteria have changed over time. In recent years there is developing consensus around the selection of a CMV seromatched donor for a HCT recipient.

Individual study results are not consistent with regards to subgroups in which this selection may be relevant. Two recent large EBMT studies report results similar to ours. In 2003, Ljungman *et al* (10) reported that a transplant from a D+ was associated with improved OS, event-free survival and decreased TRM compared to a D- in UD SCT. They did not find any difference in GVHD in the seronegative vs seropositive groups. In that study the positive effect of D+ was abrogated by TCD using ATG, but recipients receiving Alemtuzumab (as in our study) were not included. More recently the same group(11) showed an improved survival in R+ transplanted with a D+, however only in the recipients receiving myeloablative conditioning regimens. Although CMV reactivations (and GVHD) were not directly addressed, they found that deaths due to viral causes were less likely in R+/D+, leading them to suggest that the presence of CMV-specific T cells was mediating a protective effect of D+ on survival. Interestingly there was no impact of TCD noted in this study. Neither study addressed the HLA match status.

As shown in our results, the negative effect of an HLA mismatch may be abrogated somewhat by matching for CMV. The combined immunological effects as well as potential poor graft function due to treatment of CMV and an HLA mismatch (GVHD, immunosuppression and immune deficiency) are likely to be critical and may explain some of the discrepancies in earlier studies. This is supported by the fact that donor CMV serostatus does not appear to have major significance in HLA-identical sibling transplantation outcomes (10, 11) as well as the finding that CMV reactivations are higher in the setting of an HLA mismatch.(18) While the overall rates of clinically significant GVHD were low, HLA mismatching was associated with a significant increase in GVHD as expected.

Some (10, 18, 19), but not all (20, 21) studies have shown that CMV reactivation and disease are more common in the setting of a CMV mismatch (i.e. R+/D- compared to R+/D+). In the late 1980s it was reported that cells from D+ could result in better outcomes in the TCD setting through reduction in CMV disease.(22) CMV specific T cells transferred with the donor graft could protect against progressive or recurrent CMV reactivation (19, 21) and therefore be associated with better outcomes. This effect could be abrogated or lost by extensive TCD (*ex-vivo* or ATG) or the need for ongoing and intensive immunosuppression such as in GVHD.

Although, *in-vivo* TCD with Alemtuzumab was used in over 90% of the recipients in our study, it is well recognised that this does not eradicate all T cells and that a degree of CMV-specific immunity is retained in this setting. CMV specific T cells may also be of recipient origin. Peggs *et al.(23)* have recently shown that in the

316 majority of R+/D- recipients receiving TCD (mostly sibling) reduced intensity
317 conditioning (RIC) HCT, recipient-derived T cells provide protection from
318 recurrent CMV infection in the absence of GVHD. However, they stress the
319 importance of avoiding GVHD in this setting to prevent CMV-associated toxicities.
320 In our registry based study, we unfortunately do not have data on CMV
321 reactivations, immune reconstitution (IR) or the chimeric status of recipients post
322 transplant. However, in line with the findings of Peggs *et al*'s, the negative effect of
323 donor serostatus (R+/D-) in our study is seen predominantly in those recipients
324 with a co-existing HLA mismatch and consequently an increase in clinical
325 GVHD(data not shown).
326
327 Another possible mechanism for improved outcome may be through a direct (24-
328 26) or indirect (through earlier IR) (27) effect of CMV on reduction of disease
329 relapse post transplant, although this remains controversial.(28-30) Early and
330 robust IR in general has been shown to be associated with improved transplant
331 outcomes.(31) Not surprisingly, CMV specific IR has an important association
332 with a reduction in CMV reactivation and infections.(20, 32) However donor CMV
333 status has also been shown to influence the strength of IR (33) and Zhou *et al.*
334 showed that CMV specific T-cell populations from R+/D+ contained higher levels
335 of functional subsets than R+/D-recipients.(19) We found that the use of CMV
336 seronegative donors was associated with a lower relapse risk.
337
338 HLA matching is important for survival, however in contrast to our previous
339 studies, (5, 34) we did not find a similar survival between a 10/10 and 9/10
340 matched transplant, but rather findings similar to the Lee *et al.* paper (2) showing

an incremental survival disadvantage with additional HLA mismatches. Possible reasons for this include a reduction in Alemtuzumab doses in the recent era(35, 36) as well as the larger numbers now included in our study giving us greater power to detect a difference. We did see an impact of DQB1 matching on both OS and NRM. This differed from the Lee et al (2) study, however is consistent with the report from the German group(9, 37) which found a higher mortality associated with DQB1 mismatching, in particular if these mismatches were at an antigenic level. As in many studies the type of mismatch may thus be of significance and may differ in the European versus American population. Based on these differences we would recommend matching status continue to be considered for DQB1 as the impact of mismatches remains somewhat controversial. Matching should also be prioritised for HLA-B. A caution is that the number of mismatches in this study was small. Although survival was improved when either allele level or epitope matching for DPB1 was performed as has been previously shown,(4, 6) this was not a significant factor in multivariate analysis. Previously the impact has been seen most commonly in transplant pairs matched for the other HLA alleles, with less of an impact of DPB1 mismatching in ≤9/10 matched transplants and we did not perform subset analysis.

Donor age was significantly associated with transplant outcomes, although the effect in multivariate analysis was borderline. These findings are consistent with several other studies(9, 37) and suggest this factor should be taken into account in donor selection. Although donor gender and ABO matching status both had some impact on transplant outcomes in univariate analysis, these effects were not seen in multivariate analysis. Several other studies have shown conflicting results

related to these factors and it is possible that the impact may differ based on the characteristics of the population studied. In addition, small statistical effects may be more difficult to appreciate in smaller datasets.

In conclusion, our results add to the recent consensus that survival is improved by selecting a CMV matched donor for an UD HCT recipient. We significantly extend these findings by including the influence of HLA matching on this variable and suggest that these factors are closely interrelated.

Based on these results, and those from recent studies, several donor selection strategies could be proposed. A 10/10 HLA matched donor remains best and selection of a CMV matched donor is preferable. This is particularly relevant in the setting of a R+ in the HLA mismatch setting. If no D+ is available in this setting an alternative stem cell source, such as umbilical cord blood which has been shown to be associated with less GVHD, should be considered. Where a R+/D- combination cannot be avoided, active strategies to avoid GVHD should be undertaken. Finally our results suggest that donor characteristics should not be considered in isolation, but as a 'package' and individualised based on recipient characteristics.

Authorship

BES, NM, SM, JAM designed the study, collected and curated the samples and data, performed the analysis and wrote the paper. BES, NM, WB performed the laboratory typing. RS performed the statistical analysis. KK and JS collected and contributed the clinical data. BES, CA, AC, SM, DM, AP, MP, NR, KT contributed

patient data and samples. All of the authors contributed to the writing and review of the manuscript. None of the authors have any relevant conflict of interest to declare.

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Conflict of interest

None of the authors have any relevant conflict of interest to report

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540 PM2013.
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542

543 Figure legends

544

545 Figure 1: Probability of survival curves for groups based on the degree of HLA matching

546 for 10/10 alleles: 10/10 vs 9/10 vs <9/10

547

548 Figure 2: Survival curves for groups based on recipient/donor CMV serostatus and HLA

549 matching status. A. Univariate analysis, B. For an average patient from a Cox regression

550 analysis that included recipient age, disease risk, donor age, era and previous autograft.

551

552

553 Table 1: Recipient and Donor characteristics, presented by transplantation era
554

Variable	1996-1999 (N=154)	2000-2003 (N=433)	2004-2007 (N=387)	2008-2011 (N=297)	P-value (*comparison of eras)*	Overall (N=1271)
HLA Match status						
10/10	98 (64%)	286 (66%)	305 (79%)	244 (82%)		933 (73%)
9/10	41 (27%)	100 (23%)	63 (16%)	50 (17%)	<0.001	254 (20%)
<9/10	15 (10%)	47 (11%)	19 (5%)	3 (1%)		84 (7%)
HLA Match						
10/10	98 (70.5%)	286 (74.1%)	305 (82.9%)	244 (83.0%)		933 (78.6%)
9/10 A Mismatch	11 (7.9%)	18 (4.7%)	19 (5.2%)	12 (4.1%)		60 (5.1%)
9/10 B Mismatch	2 (1.4%)	11 (2.8%)	5 (1.4%)	4 (1.4%)	0.007	22 (1.9%)
9/10 C Mismatch	22 (15.8%)	48 (12.4%)	23 (6.3%)	18 (6.1%)		111 (9.4%)
9/10 DQ Mismatch	6 (4.3%)	20 (5.2%)	15 (4.1%)	12 (4.1%)		53 (4.5%)
9/10 DR Mismatch	0 (0%)	3 (0.8%)	1 (0.3%)	4 (1.4%)		8 (0.7%)
Donor age (years) median (range)	34.6 (21-53)	35.5 (19-56)	34.9 (20-60)	33.2 (19-58)	0.073	34.9 (19-60)
missing	*1*	*2*	*9*	*2*		*14*
Donor age (years)						
<30	42 (27.5%)	106 (24.6%)	130 (34.4%)	110 (37.3%)	0.001	388 (30.9%)
>30	111 (72.5%)	325 (75.4%)	248 (65.6%)	185 (62.7%)		869 (69.1%)
Duration of disease pre-sct months, median (range)	16.8 (1-245)	15.0 (2-309)	15.3 (2-381)	13.8 (2-187)	0.74	15.0 (1-381)
missing	*1*	*2*	*9*	*1*		*13*
Recipient age (years) median (range)	29.1 (2-57)	37.3 (2-66)	43.4 (1-72)	51.2 (1-71)	<0.001	40.6 (1-72)
Recipient age (years)						
<20	51 (33.1%)	108 (24.9%)	64 (16.5%)	25 (8.4%)		248 (19.5%)
20-39	68 (44.2%)	143 (33.0%)	102 (26.4%)	57 (19.2%)	<0.001	370 (29.1%)
40-59	35 (22.7%)	168 (38.8%)	182 (47.0%)	139 (46.8%)		524 (41.2%)
≥60	0 (0%)	14 (3.2%)	39 (10.1%)	76 (25.6%)		129 (10.1%)
Recipient gender						
Male	92 (59.7%)	275 (63.5%)	249 (64.3%)	184 (62.0%)	0.76	800 (62.9%)
Female	62 (40.3%)	158 (36.5%)	138 (35.7%)	113 (38.0%)		471 (37.1%)
Disease Risk – EBMT score						
Good	73 (49.3%)	184 (43.6%)	183 (48.5%)	140 (48.4%)		580 (46.9%)
Intermediate	60 (40.5%)	163 (38.6%)	138 (3.6%)	96 (33.2%)	0.19	457 (37.0%)
Poor	15 (10.1%)	75 (17.8%)	56 (14.9%)	53 (18.3%)		199 (16.1%)
Missing	*6*	*11*	*10*	*8*		*35*
Recipient / Donor CMV status						
R-/D-	82 (55.0%)	246 (57.1%)	174 (49.3%)	145 (49.2%)		647 (52.7%)
R-/D+	22 (14.8%)	36 (8.4%)	23 (6.5%)	20 (6.8%)	<0.001	101 (8.2%)
R+/D-	27 (18.0%)	88 (20.4%)	73 (20.7%)	56 (19.0%)		244 (19.9%)
R+/D+	18 (12.1%)	61 (14.2%)	83 (23.5%)	74 (25.1%)		236 (19.2%)
Missing	*5*	*2*	*34*	*2*		*43*
Recipient / Donor CMV status						
matched	100 (67.1%)	307 (71.2%)	257 (72.8%)	219 (74.2%)	0.44	883 (71.9%)
mismatched	49 (22.9%)	124 (28.8%)	96 (27.2%)	76 (25.8%)		345 (28.1%)
Missing	*5*	*2*	*34*	*2*		*43*
Stem cell source						
BM	146 (96.7%)	268 (62.3%)	122 (31.7%)	44 (14.9%)	<0.001	580 (46.0%)
PBSC	5 (3.3%)	162 (37.7%)	263 (68.3%)	252 (85.1%)		682 (54.0%)
Missing	*3*	*3*	*2*	*1*		*9*
Conditioning regimen						
Myeloablative	133 (93.7%)	268 (63.8%)	169 (43.7%)	91 (30.6%)		661 (53.0%)
Reduced Intensity	9 (6.3%)	152 (36.2%)	218 (56.3%)	206 (69.4%)	<0.001	585 (47.0%)
Missing	*12*	*13*	*0*	*0*		*25*
Previous autograft						
0	138 (89.6%)	367 (84.8%)	315 (81.4%)	259 (87.2%)	0.055	1079 (84.9%)
>0	16 (10.4%)	66 (15.2%)	72 (18.6%)	38 (12.8%)		192 (15.1%)
T-cell depletion (Campath)						
Yes	129 (94.2%)	357 (94.9%)	308 (90.6%)	246 (94.3%)	0.10	1040 (93.4%)
No	8 (5.8%)	19 (5.1)	32 (9.4%)	15 (5.7%)		74 (6.6%)
Missing	*17*	*57*	*47*	*36*		*157*

555 BM-bone marrow; PBSC-peripheral blood stem cells

Table 2: Univariate analyses of Recipient and Donor Factors on OS and NRM and relapse

	N	Survival at 5yrs (%) (95%CI)	p-value	N	NRM at 1yr(%) (95% CI)	p-value	N	Relapse at 5yrs (%) (95%CI)	p-value
Overall	1271	40.6 (38-44)	-	1236	26.5 (24-29)	-	1236	42.1 (39-45)	
HLA match status									
10/10	933	43.1 (40-47)		905	20.3 (27-23)		905	42.1 (39-46)	
1 Mismatch	254	35.6 (30-42)	0.001	247	26.1 (21-32)	0.007	247	41.5 (36-48)	0.96
>1 Mismatch	84	28.4 (20-40)		84	33.4 (24-45)		84	44.1 (34-57)	
HLA Match									
12/12	140	46.5 (38-57)		134	18.3 (13-26)		134	44.7 (36-55)	
10/10	793	42.5 (39-46)		771	20.6 (18-24)		771	41.6 (38-46)	
9/10 A Mismatch	60	36.1 (26-51)	0.011	57	24.8 (16-39)	0.16	57	41.8 (30-58)	0.97
9/10 B Mismatch	22	22.7 (11-49)		21	38.1 (22-67)		21	38.1 (21-68)	
9/10 C Mismatch	111	39.0 (31-49)		110	21.8 (15-31)		110	44.7 (36-55)	
9/10 DR Mismatch	8	46.9 (21-99)		8	12.5 (2-89)		8	25.0 (7-92)	
9/10 DQ Mismatch	53	31.7 (21-48)		51	34.9 (24-52)		51	37.8 (26-55)	
TCE-Matching status									
Match	175	41.5(34-50)		169	23.6 (18-31)		169	43.1 (36-52)	
TCEM	639	43.0 (39-47)	0.054	623	19.3 (16-23)	0.028	623	45.3 (41-50)	0.036
TCED	447	36.9 (32-42)		434	26.4 (23-31)		434	36.8 (32-42)	
HLA A									
10/10	933	43.1 (40-47)		905	20.3 (18-23)		905	42.1 (39-46)	
9/10 A match	194	35.5 (29-43)		190	26.6 (21-34)	0.14	190	41.5 (35-49)	0.99
9/10 A Mismatch	60	36.1 (25-51)	0.17*	57	24.8 (16-39)		57	41.8 (30-58)	
HLA B									
10/10	933	43.1 (40-47)		905	20.3 (18-23)		905	42.1 (39-46)	
9/10 B match	232	36.8 (31-44)		226	25.0 (20-31)	0.059	226	41.9 (36-49)	0.95
9/10 B Mismatch	22	22.7 (11-49)	0.011*	21	38.1 (22-67)		21	38.1 (21-68)	
HLA C									
10/10	933	43.1 (40-47)		905	20.3 (18-23)		905	42.1 (39-46)	
9/10 C match	143	33.1 (26-42)		137	29.7 (23-39)	0.062	137	38.8 (31-48)	0.74
9/10 C Mismatch	111	39.0 (31-49)	0.28*	110	25.8 (19-34)		110	44.7 (36-55)	
HLA DR									
10/10	933	43.1 (40-47)		905	20.3 (18-23)		905	42.1 (39-46)	
9/10 DR match	246	35.3 (30-42)		239	26.6 (22-33)	0.11	239	42.1 (36-49)	0.69
9/10 DR Mismatch	8	46.9 (18-78)	0.75*	8	12.5 (2-89)		8	25.0 (7-92)	
HLA DQ									
10/10	933	43.1 (40-47)		905	20.3 (18-23)		905	42.1 (39-46)	
9/10 DQ match	201	36.7 (30-44)		196	24.0 (19-31)	0.051	196	42.4 (36-50)	0.95
9/10 DQ Mismatch	53	31.7 (21-48)	0.03*	51	34.9 (24-52)		51	37.8 (26-55)	
Donor age (years)									
<30	388	45.3 (40-51)	0.01	376	19.2 (16-27)	0.075	376	39.5 (35-45)	0.18
≥30	869	38.6 (35-42)		846	27.9 (24-32)		846	43.6 (40-47)	
Recipient age (years)									
<20	248	45.7 (39-52)		248	21.1 (17-27)		248	40.2 (34-47)	
20-39	370	44.9 (40-50)	0.005	370	20.9 (17-26)	0.41	370	44.0 (39-50)	0.07
40-59	524	38.5 (34-43)		524	22.5 (19-27)		524	43.6 (39-48)	
≥60	129	23.5 (16-33)		129	29.2 (22-39)		129	34.5 (26-45)	
Recipient CMV									
Negative	749	44.3 (41-48)	0.013	731	20.4 (18-24)	0.057	731	42.6 (39-47)	0.66
Positive	480	35.1 (31-40)		463	25.2 (22-30)		463	42.2 (38-47)	
Donor CMV									
Negative	926	40.9 (38-44)	0.78	899	23.3 (21-26)	0.19	899	40.4 (37-44)	0.076
Positive	344	39.7 (35-46)		336	19.9 (16-25)		336	46.7 (41-53)	
Recipient / Donor CMV									
R-/D-	647	45.3 (41-49)		631	19.6 (17-23)		631	41.5 (38-46)	
R-/D+	101	37.9 (29-48)	<0.001	99	25.4 (18-36)	<0.001	99	49.1 (40-61)	0.30
R+/D-	244	30.0 (24-36)		233	32.6 (27-39)		233	38.9 (33-46)	
R+/D+	236	40.5 (34-48)		230	17.7 (13-24)		230	45.3 (39-53)	
Recipient / Donor CMV									
Matched	883	44.1 (41-48)	<0.001	861	19.1 (17-22)	<0.001	861	42.5 (39-46)	0.61
Mismatched	345	32.2 (28-38)		332	30.4 (26-36)		332	41.9 (37-48)	
Donor Sex									
Male	1022	41.1 (38-45)	0.26	989	20.9 (19-24)	0.011	989	42.0 (39-45)	0.91
Female	249	38.3 (32-45)		247	28.2 (23-35)		247	42.3 (36-49)	
Recipient / Donor Sex									
Other combination	1138	41.3 (38-44)	0.11	1103	21.4 (19-24)	0.018	1103	42.1 (39-45)	0.94
Male / Female	133	34.8 (27-44)		133	30.4 (23-39)		133	42.2 (24-52)	

Stem cell source									
BM	580	38.9 (35-43)	0.078	561	25.0 (22-29)	0.027	561	45.2 (41-50)	0.024
PBSC	682	42.2 (38-47)		666	20.4 (18-24)		666	38.7 (35-43)	
R/D ABO matching									
Match	557	40.9 (37-46)		537	20.0 (17-23)		537	42.0 (38-47)	
Minor mismatch	310	46.5 (41-53)	0.011	303	20.5 (16-26)	0.040	303	39.8 (34-46)	0.69
Major mismatch	283	33.9 (29-40)		277	29.1 (24-35)		277	42.1 (36-49)	
Bidirectional	78	36.8 (27-50)		76	22.8 (15-35)		76	46.4 (36-60)	
Duration of disease pre SCT									
<1y	532	41.7 (37-46)	0.92	579	21.6 (18-26)	0.60	579	41.3 (37-46)	0.83
>1y	736	39.9 (36-44)		704	22.7 (20-26)		704	43.1 (39-47)	
Previous autograft									
0	1079	42.9 (38-44)	0.001	1050	22.3 (20-25)	0.78	1050	40.0 (37-43)	<0.001
>0	192	27.1 (21-35)		186	22.9 (18-30)		186	54.2 (47-62)	
ERA									
96-99	154	40.8 (34-49)		148	33.8 (27-42)		148	44.2 (37-53)	
00-03	433	39.5 (35-44)	0.64	420	20.7 (17-25)	0.003	420	47.2 (43-52)	0.012
04-07	387	42.5 (38-48)		377	20.5 (17-25)		377	39.0 (34-44)	
08-11	297	37.8 (31-46)		291	21.8 (17-27)		291	35.7 (30-43)	
Disease Risk - EBMT score									
Good	580	47.5 (43-52)		563	20.2 (20-27)		563	41.6 (38-46)	
Intermediate	457	34.7 (30-40)	<0.001	444	24.5 (21-29)	0.26	444	42.6 (38-48)	0.17
Poor	199	31.7 (25-40)		194	23.6 (18-31)		194	46.0 (39-54)	
Conditioning regimen									
Myeloablative	661	41.4 (38-45)	0.33	647	24.8 (22-28)	0.016	647	41.2 (38-45)	0.71
Reduced intensity	585	40.0 (36-45)		565	19.8 (17-23)		565	42.4 (38-47)	

559 BM-bone marrow; PBSC-peripheral blood stem cells; TCE-T cell epitope; TCEM -T cell epitope match; TCED -T cell epitope
560 disparate;
561
562 *p-values are between mismatched genotype and 10/10 match
563

564 Table 3: Multivariate analysis of Survival and NRM
565

	Overall Survival			Non Related Mortality		
	N	RR (95% CI)	*p*-value	N	RR (95% CI)	*p*-value
HLA Match						
10/10 Match	878	1.00		871	1.00	
1 Mismatch	239	1.21 (1.1-1.5)	0.042	239	1.24 (0.9-1.6)	0.14
>1 Mismatch	77	1.43 (1.1-1.9)	0.016	83	1.59 (1.1-2.4)	0.028
Recipient Donor CMV						
Match	863	1.00		861	1.00	
Mismatch	331	1.40 (1.2-1.6)	<0.001	332	1.63 (1.3-2.1)	<0.001
Recipient age (years)						
<20	221	1.00				
20-39	351	1.07 (0.8-1.4)	0.57			
40-59	497	1.26 (1.0-1.6)	0.047			
>60	125	1.71 (1.3-2.3)	0.001			
Previous autos						
0	1014	1.00				
>0	180	1.42 (1.2-1.8)	0.001			
Donor Age						
<30y	372	1.00				
>30y	822	1.17 (0.98-1.4)	0.078			
ERA						
96-99	142	1.00		143	1.00	
00-03	421	0.84 (0.7-1.1)	0.18	418	0.57 (0.4-0.8)	0.002
04-07	345	0.76 (0.6-1.0)	0.049	343	0.54 (0.4-0.9)	0.002
08-11	286	0.77 (0.6-1.1)	0.078	289	0.60 (0.3-0.7)	0.001
Disease Risk - EBMT						
Good	557	1.00				
Intermediate	444	1.37 (1.2-1.6)	<0.001			
Poor	193	1.33 (1.1-1.7)	0.013			
Recipient / Donor Sex						
Other combination				1061	1.00	
Male / Female				132	1.38 (0.99-1.9)	0.063

566
567
568

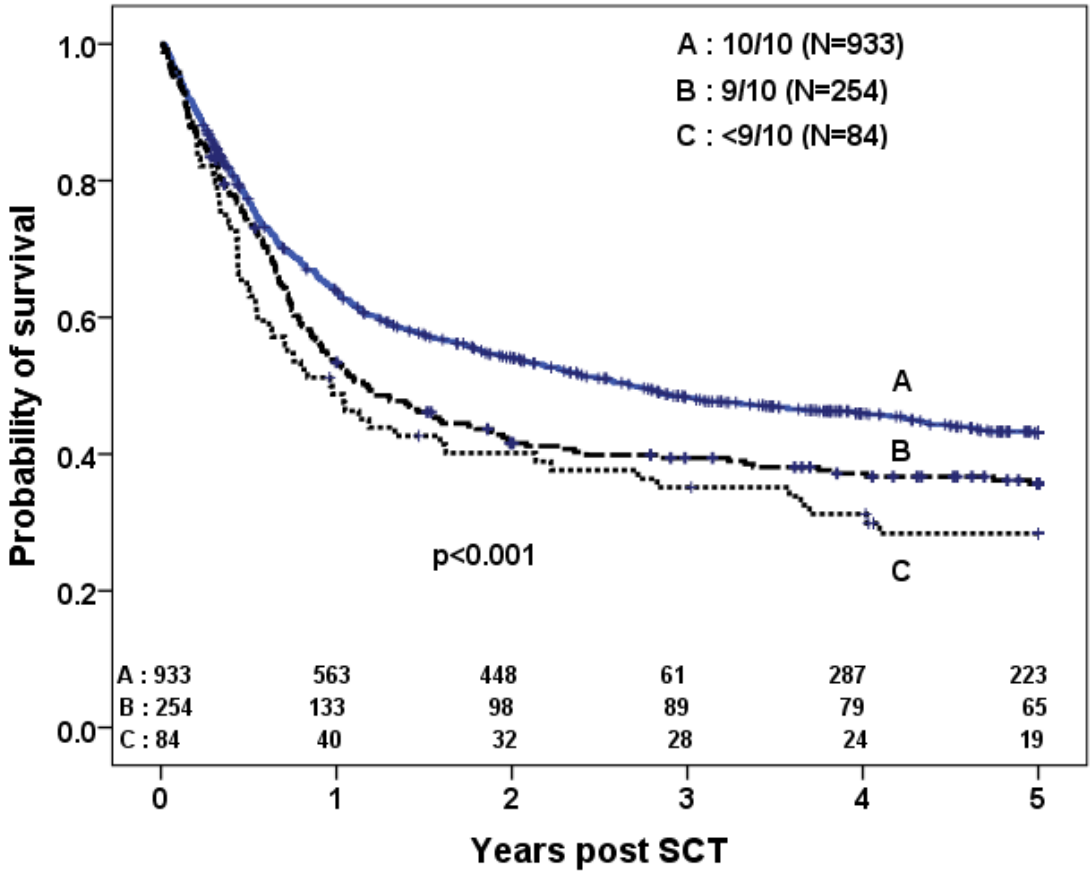
569 Table 4: Multivariate analysis of PGF, aGVHD and Relapse
570

	Primary Graft Failure			Acute GVHD grade 2-4			Relapse		
	N	OR (95% CI)	*p*-value	N	OR (95% CI)	*p*-value	N	RR (95% CI)	*p*-value
HLA Match									
10/10 Match	872	1.00		882	1.00				
1 Mismatch	233	1.7 (0.8-3.5)	0.15	237	1.52 (1.1 -2.2)	0.01			
>1 Mismatch	76	2.9 (1.2 – 7.3)	0.02	77	1.82 (1.1 – 3.0)	0.022			
Donor CMV									
Negative				875	1.00		899	1.00	
Positive				321	0.65 (0.5-0.9)	0.005	336	1.23 (1.1-1.5)	0.035
Stem cell source									
PBSC	655	1.00		542	1.00				
BM	526	4.23 (1.8-9.7)	0.001	654	0.58 (0.4 -0.8)	0.001			
ERA				134					
96-99				413	1.00		147	1.00	
00-03				372	0.31 (0.2-0.5)	<0.001	420	1.09 (0.8-1.5)	0.54
04-07				277	0.39 (0.2-0.6)	<0.001	377	0.83 (0.6-1.1)	0.21
08-11					0.28 (0.2-0.5)	<0.001	291	0.70 (0.5-0.9)	0.031
Conditioning type									
Reduced Intensity	554	1.00							
Myeloablative	627	8.2 (2.5-27.2)	0.001						
Previous autos									
0							1049	1.00	
>0							186	1.55 (1.2-1.9)	<0.001

571

572

Figure 1


A : 10/10 (N=933)
B : 9/10 (N=254)
C : <9/10 (N=84)
Probability of survival
1.0
0.8
0.6
0.4
0.2
0.0
A
B
C
p<0.001
A : 933 563 448 61 287 223
B : 254 133 98 89 79 65
C : 84 40 32 28 24 19
0 1 2 3 4 5
Years post SCT

582 Figure 2a

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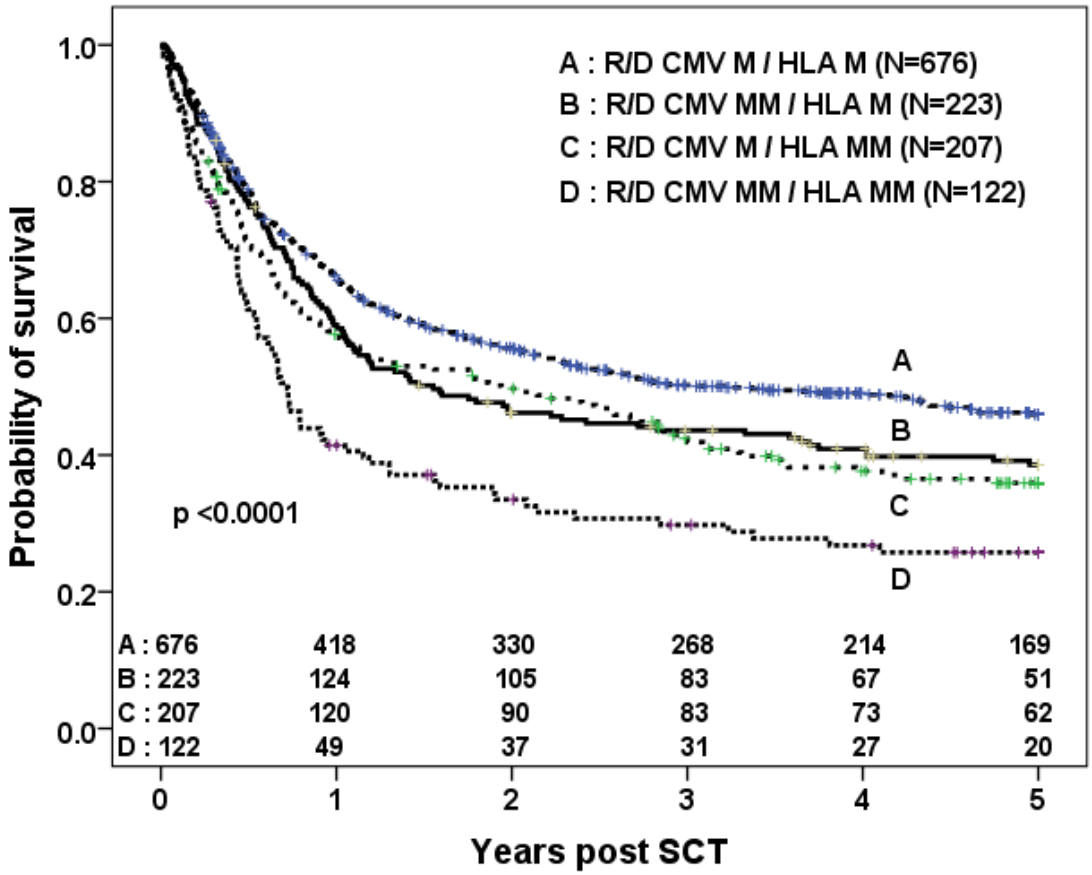

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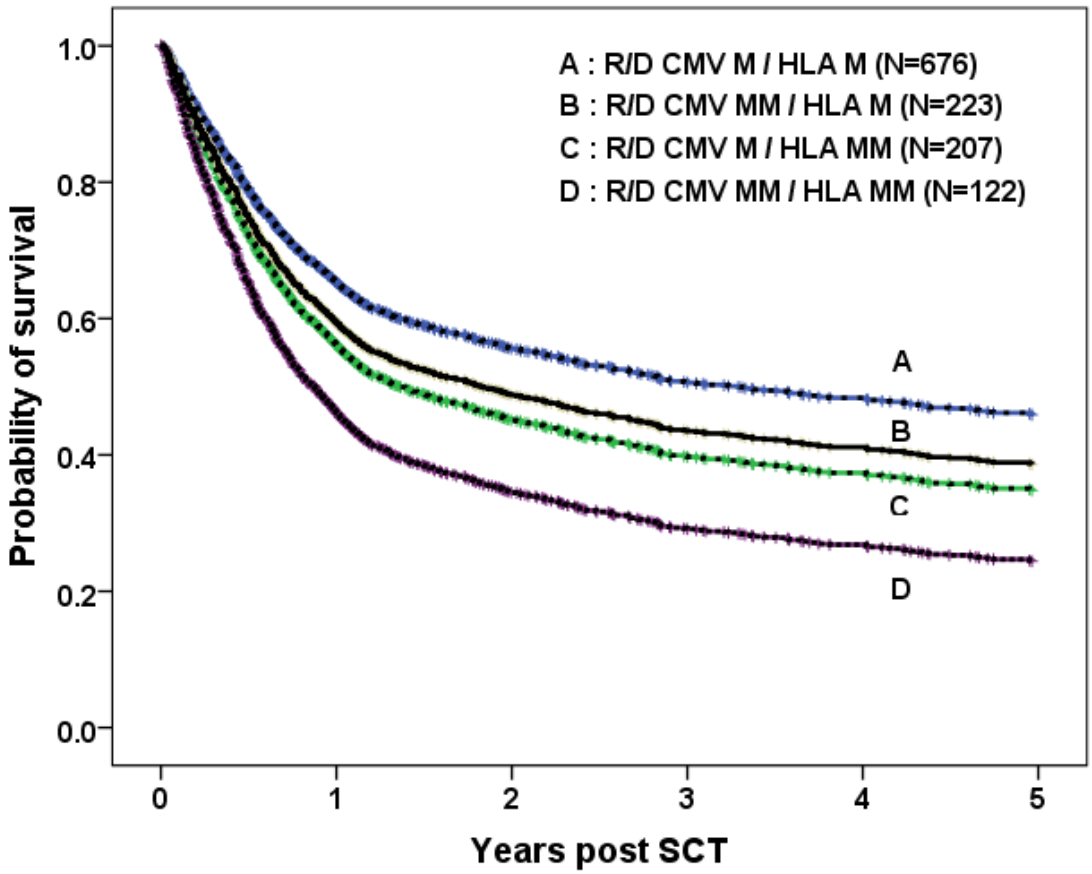

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