The impact of donor factors on primary non-engraftment in recipients of reduced intensity conditioned transplants from unrelated donors

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Background and Objectives. Primary graft failure is a serious complication following hematopoietic cell transplants, particularly when using unrelated donors. We analyzed factors affecting primary graft failure in recipients of hematopoietic cell transplants from unrelated donors, which were performed using reduced intensity conditioning.

Design and Methods. This was a retrospective analysis of 144 patients whose transplants took place between March 1998 and October 2004. The data were analyzed in January 2005.

Results. The median age of the patients was 51 years. The diagnoses were varied. Conditioning regimens were fludarabine, melphalan, campath (n=80), fludarabine, busulphan, campath (n=38), fludarabine, BEAM, campath (n=9) and other (n=17). The donor was 10/10 allele matched in 95/144 (66%) cases; 94 donated bone marrow and 50 peripheral blood stem cells. The 3-year probability of overall survival was 43%. The median follow-up was 724 days (range: 91-1651 days). Of evaluable patients, 7/140 (5%) failed to achieve myeloid engraftment. Primary graft failure was significantly associated with the use of a mismatched donor (6/47,13% versus 1/93, 1%, p=0.006), as well as: bone marrow as the source of stem cells (p=0.046), chronic myeloid leukemia compared to other diagnoses (p=0.022), and a female rather than a male donor (p=0.019). In multivariate analysis chronic myeloid leukemia, HLA mismatched and/or female donors remained significantly associated with primary graft failure. Single HLA mismatches were tolerated, however in multiply mismatched grafts, overall survival was worse (p=0.005); transplanted-related mortality (p=0.005) and chronic graft-versus-host disease (p=0.025) were increased.

Interpretation and Conclusions. These data have implications for the choice of donor and stem cell source in transplants performed using reduced intensity conditioning regimens, suggesting that the use of bone marrow, female donors and HLA-mismatched grafts increase the risk of primary graft failure, and should be avoided in certain situations.

Key words: reduced intensity conditioned, unrelated donors, primary non-engraftment.

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Hematopoietic cell transplants are now a recognized curative treatment for a number of hematopoietic malignancies. Various advances in the field have extended the applicability of this procedure to more diverse groups of patients. Such advances include the improvement in tissue typing methods and the understanding of the impact of HLA matching on transplant outcome. This has allowed for the safer use of unrelated donors in the more than 70% of patients who do not have matched siblings. The creation of large and well-managed registries of unrelated donors has increased the efficiency with which these donors can be sought and utilized.[1] Another advance has been the development of reduced intensity conditioning regimens, which aim to reduce transplant-related mortality, but maintain the disease control by exploiting the graft-versus-malignancy effect.[2,3] Analysis of transplants using these conditioning regimens has shown that they are able to induce stable engraftment and result in lower toxicity.[4,5] This has allowed transplants to be offered to an older group of patients and to those with co-morbidities.

Primary graft failure, although now a relatively rare complication following hematopoietic cell transplants, nevertheless constitutes a serious problem associated with morbidity and mortality.[6] This may be particularly problematic in the setting of transplants from unrelated donors, when considering the possibility of second grafts, with the associated logistic and financial implications. It is important to avoid or at least minimize any known factors which may be likely to increase the incidence of this complication without

compromising care. There are not yet many data on the outcome of reduced intensity conditioning transplants from unrelated donors, in particular with regards to what degree of HLA matching is required to achieve a satisfactory outcome. The older patients who generally undergo this form of transplant are less likely to have a fit, HLA-matched sibling and thus more likely to need an unrelated donor. We analyzed the outcome of 144 recipients of hematopoietic cell transplants from unrelated donors to assess the impact of this variable.

Design and Methods

Patients

The patients included in this retrospective analysis had received a transplant for a hematologic malignancy, at a UK transplant center, using an unrelated donor and a reduced intensity conditioning regimen. The patients were recruited from two sources: 62 came from a single UK center and 82 were from various centers within the UK where donors were provided by the Anthony Nolan Trust (ANT) (data were collected by the ANT from the Transplant Centers in these cases). The decision to use reduced intensity conditioning was made by the individual transplant physicians. The transplants took place between March 1998 and October 2004. The characteristics of the patients and donors are shown in Table 1. The median age of the patients was 51 years (range: 12-66) and that of the donors was 36 (range: 21-56). The data were analyzed on 12/01/2005. Appropriate ethical permission was obtained and all patients and donors signed informed consent prior to transplant/donation.

Definitions

Patients with early stage disease included those in first complete remission from acute leukemia, those in first chronic phase of chronic myeloid leukemia, previously untreated myelodysplastic syndrome and those with lymphomas in first complete remission or very good partial remission.

HLA matching was considered at 10 alleles (i.e. HLA–A,–B,–C,–DRB1,–DQB1). This was high resolution matching in over 85% of pairs and medium or low resolution in the remainder. In two pairs the HLA–C type was unknown.

Conditioning

Conditioning consisted of fludarabine (150 mg/m^2), melphalan (140 mg/m^2) and campath (FMC) in 80 patients, fludarabine (150 mg/m^2), busulphan (8 mg/m) and campath (FBC) in 38 patients, fludarabine (90 mg/m^2), BEAM (30 mg/m^2, cytarabine 1600 mg/m^2, etoposide 800 mg/m^2, melphalan 140mg/m^2) and campath (fBEAMc) in 9 patients and various other regimens in the remaining 17 patients. The dose of campath differed depending on the center and was either 50 mg or 100 mg. All patients received T-cell depleting agents (usually campath-1H) as part of the conditioning regimen. In three cases no additional graft-versus-host disease (GvHD) prophylaxis was used, while in 93 (65%) cases cyclosporine was used in addition and in 42 (29%) cases both cyclosporine and methotrexate were used (Table 1).

Table 1. Characteristics of the patients and donors.

Characteristics	*Number (percentage)*
Patient gender	
Male	90 (63%)
Female	54 (36%)
Donor gender	
Male	118 (82%)
Female	26 (18%)
Patient CMV status	
Positive	64 (44%)
Negative	79 (55%)
Unknown	1 (1%)
Donor CMV status	
Positive	40 (28%)
Negative	104 (72%)
Disease	
Chronic myeloid leukemia	14 (10%)
Acute myeloid leukemia	37 (26%)
Acute lymphoblastic leukemia	2 (1%)
Chronic lymphocytic leukemia	12 (8%)
Hodgkin's disease	11 (7%)
Non Hodgkin's lymphoma	33 (23%)
Myelodysplasia	18 (13%)
Plasma cell dyscrasia	13 (9%)
Myeloproliferative disease	4 (3%)
Disease stage	
Early	71 (49%)
Late	60 (42%)
Relapse	13 (9%)
GvHD prophylaxis	
Cyclosporine alone	93 (65%)
Cyclosporine/methotrexate	42 (29%)
None	3 (2%)
Other	2 (1%)
Unknown	4 (3%)
Stem cell source	
Bone marrow	94 (65%)
Peripheral blood stem cells	50 (35%)
HLA matching status*	
Match	95 (66%)
Class I mismatch	37 (26%)
Class II mismatch	4 (3%)
Class I and II mismatch	8 (5%)

**Considers 10 HLA alleles at HLA–A,–B,–C,–DRB1,–DQB1.*

Statistical analyses

Statistical analyses were performed using SPSS (v.10.0) software (SPSS Inc., Chicago, USA). Associations were tested using the χ^2 test (or Fisher's exact test for those analyses involving low numbers). Time-dependent analyses (overall survival, chronic GvHD and disease relapse rates) were analyzed using Kaplan-Meier methods[7] and were compared using the log-rank statistic. Probabilities are given for outcomes at three years unless otherwise stated. Multivariate analysis of time-dependent variables was performed using Cox regression analysis. Multivariate analysis of variables that were not time-dependent was performed using logistic regression analysis. The patients' and donors' ages were grouped for analysis, using the median age as a cut-off. In all univariate analyses the following factors were considered: patients' and donors' age, gender and cytomegalovirus status, disease and stage at transplant, conditioning regimen, GvHD prophylaxis, stem cell source and HLA matching status.

Results

Engraftment

Five percent (7/140) of all patients had primary graft failure (defined as failure to achieve a neutrophil count of 0.5×10^9/L before death or necessitating a second stem cell infusion in patients who survived at least 28 days after transplant). Of these, five had autologous rescue, one received a second stem cell infusion from the same unrelated donor (first donation bone marrow, second peripheral blood stem cells) and one died prior to any additional infusion of cells.

Primary graft failure was significantly associated with the use of a mismatched donor (6/47,13% versus 1/93, 1%, p=0.006). All of these mismatches were at class I loci (in addition there was no difference depending on whether the mismatches involved single or multiple loci). None of the patients with mismatches at class II loci suffered primary graft failure. Other factors associated with primary graft failure were: use of bone marrow rather than peripheral blood stem cells as the source of hematopoietic cells (7/91, 8% versus 0%, p=0.045), transplant for chronic myeloid leukemia rather than for other diagnoses (3/14, 21% versus 4/126, 3%, p=0.022), and the use of a female versus male donor (4/25, 16% versus 3/115, 3%, p=0.019). There was a trend towards an increase in primary graft failure among patients receiving grafts from older donors (6/71, 8% versus 1/68, 1%, p=0.065). In contrast, patient gender, patient age, disease stage, conditioning regimen and drugs used for GvHD prophylaxis did not significantly affect primary graft failure. In multivariate logistic regression analysis, receiving a transplant for chronic myeloid leukemia, the use of HLA mismatched donors and the use of a female donor retained significance (Table 2). Unfortunately, information on the number of CD34 cells in the product was not available for the entire cohort. However, we were able to analyze the effect of this variable in the single center cohort (62 pairs). CD34 counts under 2×10^6/kg were associated with a significantly worse rate of engraftment, with all of those in this cohort who failed to achieve engraftment (four patients) falling into this category (p<0.001). The numbers of CD34 cells were significantly associated with the type of donation. The median number of CD34 cells in bone marrow grafts was 2.48×10^6/kg (range: 1-14.09×10^6/kg) while the median number of CD34 cells in peripheral blood stem cell grafts was 7.1×10^6/kg (range: 3.11-18.20×10^6/kg). None of the peripheral blood stem cell collections had fewer than 2×10^6 CD34 cells/kg (compared to 12/36, 33% in the bone marrow grafts) and 22/26 (84.6%) of the peripheral blood grafts contained more than 4×10^6 CD34 cells/kg (compared to 8/36, 22% in the bone marrow grafts). Female donors were more likely to yield a CD34 cell number under 2×10^6/kg (3/10, 30%) than were male donors (9/52, 17%), and less likely to yield a CD34 cell count over 4×10^6/kg (3/10, 30%) compared to male donors (27/52, 52%). These differences did not reach statistical significance.

Table 2. Multivariate analysis of factors affecting the rate of primary graft failure.

	p value	*HR*	*95.0% C.I.*	
			Lower	*Upper*
HLA mismatch	0.028	0.057	0.004	0.739
Female donor	0.048	0.144	0.021	0.984
Stem cell source	0.803	4159.595	0.000	e
Chronic myeloid leukemia	0.013	15.794	1.788	139.495

The median time to engraftment was 15 days after stem cell infusion (range=10-53 days). Factors significantly associated with faster engraftment were conditioning regimen and type of GvHD prophylaxis. Engraftment was faster in those receiving FMC (median: 14 days) than in those receiving FBC (median: 18 days) or fBEAMc (median:16 days), log rank, p=0.0004. Likewise, engraftment was faster in those who received cyclosporine alone (median: 14 days) than in those who received cyclosporine and methotrexate (median: 18 days), log rank p=0.001. There was no significant impact from receiving

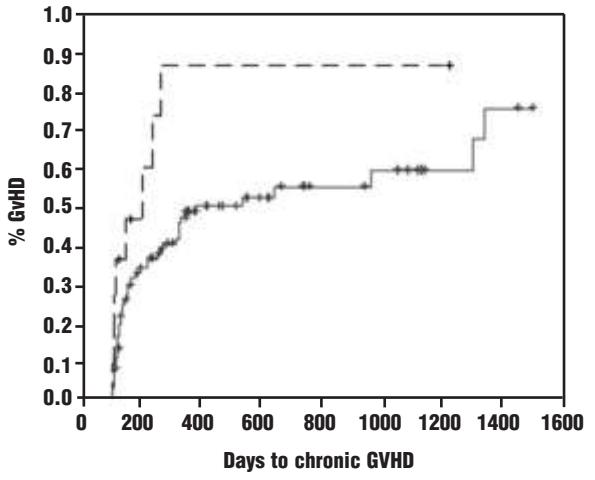

Figure 1. The incidence of chronic GvHD was dependent on HLA matching status. There was a significant increase in the multiply mismatched pairs (- -) compared to pairs which were matched or had a single HLA mismatch (–) (p=0.025).

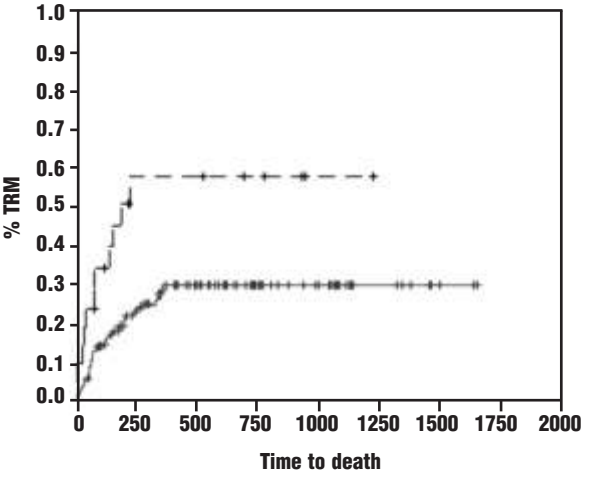

Figure 2. The incidence of transplant-related mortality at one year was dependent on HLA matching status. There was a significant increase in the multiply mismatched pairs (- -) compared to pairs which were matched or had a single HLA mismatch (–) (p=0.004).

peripheral blood stem cell or HLA mismatched grafts.

Acute graft-versus-host disease

The overall incidence of acute GvHD in this cohort was 41% (55/133). This was grade I in 34 cases, grade II in 18 cases and grade III in three cases. There were no cases of grade IV disease. The type of conditioning regimen used was associated with a significant difference in the incidence of acute GvHD. The incidence was higher in those receiving FMC (39/74, 52%) than in those receiving FBC (10/37, 27%) or fBEAMc (1/7, 14%), p=0.023. There was a trend towards an increase in acute GvHD in recipients of peripheral blood stem cells compared to bone marrow (p=0.084). No other individual factor, including type of GvHD prophylaxis or HLA matching status, influenced the incidence of this complication.

There was, however, a trend towards an increase in grade II and III acute GvHD in those who were mismatched for class II loci alone (2/4, 50%), or class I and II loci (2/7, 29%), compared to pairs who were HLA matched (14/92, 15%) or mismatched only for class I loci (2/30, 7%), p=0.091. No other patient, donor or transplant-specific factors were significantly associated with the severity of acute GvHD.

Chronic graft-versus-host disease

Of those patients who engrafted, 109 were alive at day 100 and therefore eligible for analysis of chronic GvHD. The 3-year probability of chronic GvHD was 62%. This was reported to be limited in 36 (62%) cases and extensive in 22 (38%) cases. In just over half of the patients (30, 52%) the chronic GvHD was preceded by acute GvHD. There was no significant difference in the extent of chronic GvHD depending on whether this followed acute GvHD or arose *de novo*. Of this cohort, 40 patients received donor lymphocyte infusions. The median time to donor lymphocyte infusion was 254 days (range 63-1304 days). Among 50 recipients of peripheral blood stem cells, two required donor lymphocyte infusions (24%) whereas among the 91 transplanted using bone marrow, 28 required infusions (31%). This difference was not significant. Of 40 patients receiving donor lymphocyte infusion, 27 (65%) were reported to have developed chronic GvHD at some time. This was extensive in 10 cases. Patients who developed GvHD following donor lymphocyte infusions are included in the analysis of chronic GvHD.

In time-dependent analysis, patients with two or more HLA loci mismatched were significantly more likely to develop chronic GvHD than those who were HLA matched or had a single locus mismatched (log rank, p=0.025) (Figure 1). The use of peripheral blood stem cells was associated with a significantly higher risk of chronic GvHD when compared to bone marrow (p=0.002). In addition the use of peripheral blood stem cells was significantly more likely to result in extensive disease (14/27, 52%) than was the use of bone marrow (8/31, 26%), p=0.041. No other patient, donor or transplant-specific factors were significantly associated with the incidence of chronic GvHD.

Transplant-related mortality

The transplant-related mortality was 17% at day 100 and 33% at one year. The presence of two or more HLA mismatches in the graft was associated with a significantly higher transplant-related mortality at one year than that associated with a single mismatch or matched HLA (p=0.004) (Figure 2). There was no significant difference between the pairs

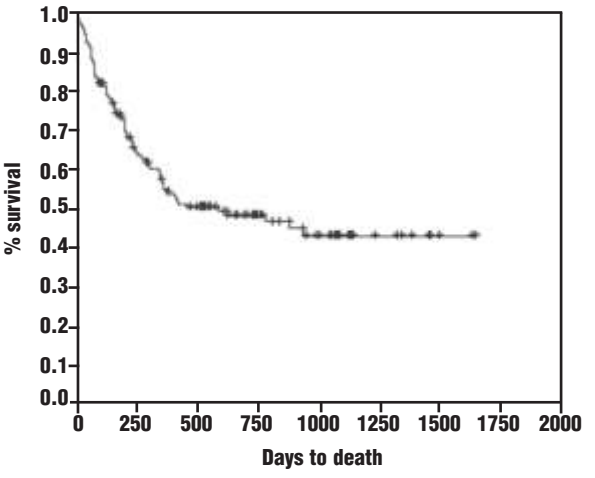

Figure 3. Overall survival in 144 recipients of unrelated donor transplants using reduced intensity conditioning regimens.

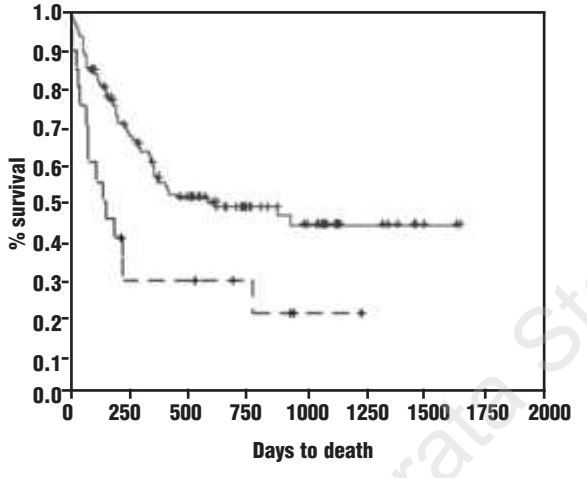

Figure 4. Overall survival was dependent on HLA matching status. There was a significant survival detriment in the multiply mismatched pairs (- -) compared to pairs which were matched or had a single HLA mismatch (–) (p=0.005).

which were HLA matched and those in which a single locus was mismatched.

Disease relapse

All patients who engrafted were eligible for analysis of disease relapse. The 3-year probability of relapse was 62%. The only factor to be significantly associated with an increase in disease relapse was receiving a transplant for relapsed disease compared to all other stages (p=0.027). Neither the presence of acute nor chronic GvHD was significantly associated with a decrease in the relapse rate.

Survival

The 3-year probability of overall survival was 43%, with a median follow up of 724 days (range: 91-1651 days) (Figure 3). In this cohort the only variable significantly affecting overall survival was HLA matching status. Survival was worse in recipients of grafts with two or more HLA mismatches than in recipients of grafts with a single mismatch or matched HLA (p=0.005) (Figure 4).

There was a trend to better overall survival in those patients who developed limited chronic GvHD (as compared to those who did not develop chronic GvHD or who developed extensive disease), p=0.079. The occurrence of primary graft failure or acute GvHD did not have a significant impact on overall survival.

Discussion

These data extend the findings of earlier smaller reports, showing the feasibility of using unrelated donors in the setting of reduced intensity conditioning transplants.[4,8-10] Although the follow-up at this time is relatively short, there are certainly a number of patients who remain alive and disease-free for a significant period following their transplant (median 622 days, range 92-1637), suggesting that some patients may be cured by this procedure.

The median age of the patients in this cohort was 51 years. There were no significant differences in any of the transplant complications studied when comparing patients older than the median with those younger. At least two previous studies have drawn similar conclusions,[10,11] supporting the view that age *per se* should no longer be an absolute contraindication to transplantation. This is particularly helpful information in the setting of transplants from unrelated donors, as many older patients do not have a fit HLA-matched sibling to act as the donor.

The 3-year probability of overall survival was 43% in this mixed cohort of patients of whom more than half had late stage disease. The only factor resulting in a significant survival detriment was the presence of two or more HLA mismatches in the graft. It has previously been reported in the myeloablative transplant setting that a single HLA mismatch may be well tolerated.[12] In many cases those with multiply mismatched loci included pairs with mismatches at both class I and II loci, a situation well recognized to result in a poorer outcome.[12] This highlights the need for high resolution tissue typing prior to transplantation, as many mismatches may be *hidden* if only serological/medium resolution typing is performed.[1]

The main reason for the decreased overall survival in recipients of multiply HLA mismatched grafts was the increase in transplant-related mortality. The transplant-related mortality at one year was 58% in the mismatched pairs, but only 30% in the pairs who

were matched (or had a single HLA mismatch). The cause of death in the majority of these cases was unrelated to GvHD. In fact only three deaths were directly attributable to GvHD; in two patients this was acute following donor lymphocyte infusions and in the third it was extensive chronic GvHD (without preceding acute GvHD). In fact the occurrence of severe, acute GvHD was extremely rare. Although 41% of patients developed acute GvHD, it was scored as greater than grade II disease in only three cases. Two factors are likely to have contributed to this. First, reduced intensity conditioning transplants have been reported to result in a lower incidence of acute GvHD due to (among other reasons) limited tissue injury at the time of conditioning and differences in the type of immunosuppression used.[13] Second, the use of campath as a T-cell depleting agent is very effective in reducing the incidence of acute GvHD (especially severe disease) in the context of transplant protocols involving reduced intensity conditioning.[14-16] The fact that HLA matching was not seen to have any impact in this context is, therefore, not surprising; however, the relatively small number of mismatched pairs in the study (especially for class II loci) should also be borne in mind.

Conversely, chronic GvHD remained a problem in these patients, with a 3-year probability of chronic GvHD of 62% and one third of the cases being extensive disease; it should, however, be appreciated that a number of these patients received donor lymphocyte infusions, prior to which they did not have GvHD, and hence the high incidence of chronic GvHD cannot be related to risk due to the initial transplant alone. Multiply HLA mismatched pairs and those who received peripheral blood stem cell grafts were significantly more likely to develop this complication. Interestingly, HLA matching did not influence the severity of chronic GvHD, while those receiving peripheral blood stem cells had a greater chance of developing extensive disease. The association of peripheral blood stem cell grafts with chronic GvHD is well recognized in the setting of sibling transplants,[17-19] and extensive chronic GvHD has been shown to be more common in recipients of peripheral blood stem cells from unrelated donors.[20] There was a trend towards a survival advantage in those with limited chronic GvHD only, compared to those with no chronic GvHD or those with an extensive form of the disease. Although this could not be shown to influence the relapse rate, this may be due to the small numbers in this group.

Sustained neutrophil engraftment is a prerequisite for the successful outcome of a hematopoietic cell transplant. Primary graft failure results in major morbidity and mortality and, particularly in the context of transplants from unrelated donors, has both logistic and financial implications. Reduced intensity conditioning has been shown to be sufficient to result in durable engraftment[4,21] in the setting of grafts from unrelated donors. The incidence of primary graft failure (5%) in the current report is relatively low (and comparable to rates seen using unrelated donors in myeloablative transplants)[6,22] and is lower than that seen in a number of other reduced intensity conditioning studies using unrelated donors.[23,8] This may be related in part to the widespread use of campath in this cohort which has been shown to be associated with high rates of engraftment.[15]

The most important alterable variable we found to be implicated in primary graft failure was the presence of a class I HLA mismatch in the graft. This has previously been reported in the myeloablative transplant setting.[22,24] In this cohort there did not appear to be any difference dependent on whether the mismatch was single or multiple i.e. a single allele mismatch was sufficient to result in this complication. It has also been reported in the myeloablative setting that antigenic mismatches are more likely to result in primary graft failure than are allelic mismatches.[25] In the current cohort this finding was not borne out. Two of the pairs with a single mismatched allele had antigenic mismatches and two had allelic mismatches. Although not many studies on reduced intensity conditioning transplants have reported on these parameters specifically, some have shown similar trends towards increased primary graft failure in HLA mismatched transplants,[9] whilst other have not.[8] A possible reason for this may lie in others differences between the studies (e.g. the number of HLA mismatched pairs and the proportions of peripheral blood stem cell and bone marrow recipients). In the current study no patients who received peripheral blood stem cells failed to engraft (despite 20% being mismatched for class I loci), thus it is possible that peripheral blood stem cells may *override* the effect of an HLA mismatch. One group showed a very high rate of primary graft failure in recipients of unrelated non-myeloablative transplants (27%) in a study in which the majority of the patients had received bone marrow.[26]

In our group a relatively high percentage (65%) of patients received bone marrow-derived stem cells, unusual in the setting of reduced intensity conditioning. The reason for this was the initial reluctance of the UK registries to sanction the use of granulocyte colony-stimulating factor in normal donors (due to ethical reasons), until such time as the safety of this procedure was ascertained. The benefit from using peripheral blood stem cells is likely to result from the numbers of cells (total white cells, CD34 and T cells) which are present in this type of graft[27-29] and it is well recognized that engraftment is influenced by the

numbers of CD34 cells infused.[30,31]

Unfortunately data on the CD34 cell count were not available for all patients in this study. However, in the subgroup in which CD34 counts were available, there was a significant association between primary graft failure and low CD34 cell counts ($<2\times10^6$/kg) and a clear association between CD34 numbers and the type of donation.

This same factor may explain our findings that the use of female donors and older donors was associated with an increase in primary graft failure. It has been shown that female donors yield fewer stem cells than do male donors.[32] Another factor which has been shown to have an effect on primary graft failure is the number of $CD3^+$ cells in the graft; however, it was not possible to analyze this variable in the current data set.[33]

The only non-donor-related factor which was found to result in an increase in primary graft failure was receiving a transplant for chronic myeloid leukemia. This has been shown in a number of previous studies,[34,35,22,8] although the reason for this is not entirely clear. Nevertheless, this does influence the risk which can be discussed with individual patients prior to transplant.

Although in this study we did not show a statistically significant decrease in overall survival in those who failed to engraft, this has been shown in other studies.[8] Irrespective of a statistical survival benefit, at best the patient has endured a *failed transplant* (with the co-existing morbidities) after which they are returned to their previous disease status. Six of the patients with primary graft failure in this study had autologous re-infusion of stem cells. Two of these have since died of progressive disease. One patient (with a single antigenic HLA–A mismatch) failed to engraft following an infusion of bone marrow containing a low number of stem cells (CD34 count 1.32×10^6/kg) for myelodysplasia. After a protracted period she was able to receive a second donation of peripheral blood stem cells (CD34 count 5.45×10^6/kg) from the same donor following which she successfully engrafted (on day 11).

The picture of an *unfavorable* donor begins to emerge from these data. They suggest that a single HLA mismatch may be tolerated (as in the myeloablative setting) with regards to GvHD, transplant-related and overall survival, but not with regards to primary graft failure in certain settings (e.g. in the context of bone marrow grafts). It seems logical that if one other risk factor for primary graft failure exists (e.g. chronic myeloid leukemia), the use of a donor who presents a second risk factor (HLA mismatch, female) should be contemplated with caution. Thus, despite encouraging results in general using unrelated donors in this treatment modality, there remain situations in which, despite a suitable patient, the donor characteristics are such as to urge caution in proceeding with the transplant.

All authors contributed to the conception and writing of the maniscript.

BES is the author taking primary responsibility for the paper and created all the Tables and Figures. The authors also declare that they have no potential conflicts of interest.

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