Allogeneic haematopoietic stem cell donation and transplantation across the MHC class I barrier: "Faster is better than more. More is better than less".

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How to improve the search for an unrelated haematopoietic stem cell donor. Faster is better than more!

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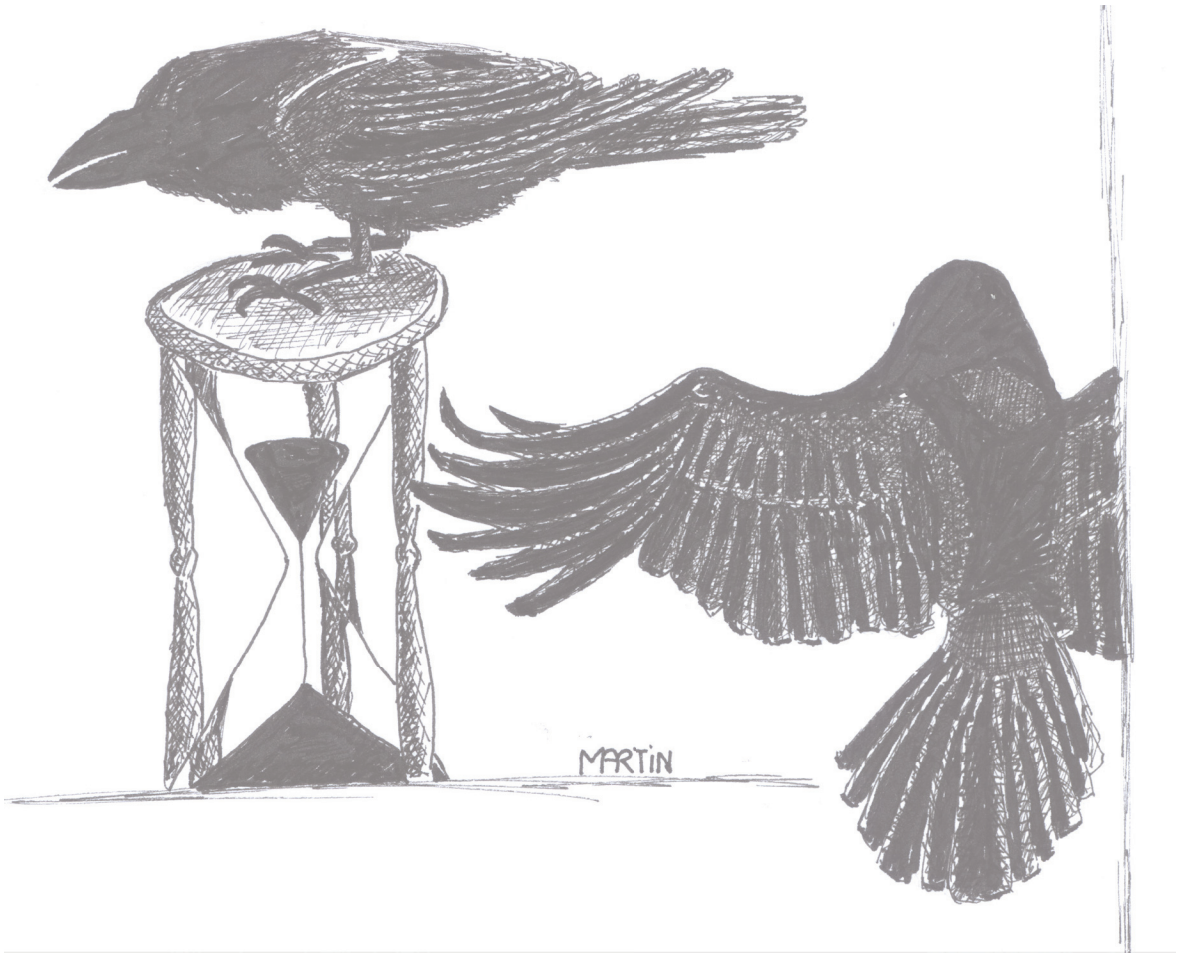
Bone Marrow Transplantation. 2005; 35:645-652



Why wait for the ravens

Abstract

Many patients do not reach haematopoietic stem cell transplantation. Shortage of unrelated donors is still seen as the main cause. However, with a world wide unrelated donor pool containing more than 8 million donors, it is possible that other impediments are becoming more important.

We analysed 549 unrelated donor searches for Dutch patients, performed between 1987 and 2000, in order to find the reasons for failure or success to reach transplantation.

Between 1996 and 2000, 59% of the patients of Northwest European origin received a graft from an unrelated donor with a median time span of 4.4 months from the start of the search. Eleven percent of the patients lacked a compatible donor, while 30 percent became medically unfit for transplantation. This in contrast to the patients of non-Northwest European origin for whom unrelated donor shortage is still the most important impediment; only 32% were transplanted while 50% lacked a compatible donor.

We conclude that the shortage of donors is no longer the biggest constraint in unrelated stem cell transplantation for patients of Northwest European origin. It may be more effective to optimise the chance on transplantation by making the search process more efficient.

Introduction

Haematopoietic stem cell transplantation is the therapy of choice for an increasing number of malignant and non-malignant haematological diseases.[1] For successful transplantation, a donor who is identical for Human Leukocyte Antigen (HLA) or, if not available, nearly identical, is considered to be acceptable. Approximately one third of the patients have an HLA identical sibling donor. The remaining patients are dependent on the availability of either an acceptable unrelated donor (UD), an unrelated cord blood unit or a family donor (other than an HLA identical sibling). The number of allogeneic stem cell transplantations has increased over the years, as well as the number of patients who were eligible for an allogeneic stem cell transplantation.[2] This was mainly due to the reduction of transplant related mortality in the last decade. Additionally, stem cell transplantation is considered a therapy of choice for an ever-increasing number of diseases.

Since the start of Bone Marrow Donors Worldwide (BMDW) in the late eighties, the number of available stem cell donors has increased from a few hundred thousand to over 8 million.[3] In spite of the increased donor pool, there is still a significant percentage of patients worldwide in need of haematopoietic stem cell transplantation, who do not receive a graft.[4-10] The lack of acceptable donors always has been considered to be the primary cause of the failure to transplant.[11] However, it is possible that apart from an insufficient number of UD there are other impediments in the donor search process.

We analysed the UD searches for Dutch patients, performed between 1987 and 2000, with the ultimate aim to identify parameters in the search process which, when improved, may heighten its effectiveness in the Netherlands and elsewhere.

Material and methods

The patients

UD searches performed between 1987 and 2000 for 644 patients from Dutch transplantation centres formed the data set to be analysed and includes all paediatric patients but only a proportion of the adult patients in the Netherlands. Two transplantation centres treating adult patients were not included as their unrelated donor selection was not performed by Europdonor during the studied period and their selection criteria were different to those of Europdonor. Patients who were registered but for whom intention for treatment was revoked, were excluded from the study. This group (n=96, 15%) includes all patients who were actively withdrawn from the search because of reasons not related to the search process, such as: personal reasons, the patient not reaching remission, change in treatment preference i.e. antithymocyteglobulin treatment for Severe Aplastic Anaemia (SAA), autologous transplant for other reasons than lack of UD and availability of stem cells from a genetically identical

sibling born after the start of the UD search. This group was equally distributed across the sexes, diagnoses, ethnic groups and age groups.
The remaining 548 patients originated from the following Dutch transplantation centres: Leiden University Medical Centre in Leiden (n=362), Erasmus MC/Daniel den Hoed in Rotterdam (n=148), and University Medical Centre, Wilhelmina Children's Hospital, in Utrecht (n=38). The group of patients was divided into a paediatric group, patients with an age below 16 years (n=275), and an adult group containing patients 16 years of age or older (n=273).
The period in which unrelated donor searches were started was subdivided as follows: 1987-1990, 1991-1995 and 1996-2000. Between 1987 and 1990 the three clinics performing unrelated transplants coordinated the searches themselves, with Europdonor in an advisory role, while from 1991 onwards Europdonor was responsible for the searches for all transplant centres mentioned above. In 1996 high resolution HLA typing was introduced for all UD searches. The patients' characteristics are shown in Tables 1a and 1b. The analysis was done separately for the patients of Northwest European origin (n=462), and patients of non-Northwest European origin (n=86). The first group includes patients originating from Germany, the Netherlands, Belgium, Luxemburg, Great Britain, Ireland, and Scandinavia and is well represented in Bone Marrow Donors Worldwide in contrast to non-Northwest European Caucasians. The latter group was a mixture of patients of which the majority originating from Turkey (n=20), Morocco (n=9), Indonesia (n=9), Surinam (n=7), Dutch Antilles (n=6) and a variety of other countries.

Search strategies

The outline for the donor search process for a patient who lacks an HLA (genotypically) identical sibling was as previously described.[6] In short, after a patient was reported to Europdonor, a UD search was started by looking in BMDW for an HLA-A, -B, -DR broad- or if possible split-identical donor. The broad antigens are those antigens, which can be subdivided by serological techniques into two or more so-called split antigens, e.g. HLA-B5 contains the splits HLA-B51 and HLA-B52. If none was found, a five out of six antigen matched donor was looked for. The number of HLA-A, -B, -DR split typed donors requested for high resolution HLA typing was based on the frequency of the patients HLA phenotype in BMDW and the urgency of the search (medium: 5, range: 3 – 9). If possible a higher number of potential donors are requested for patients with a less common HLA phenotype and/or high transplantation urgency. If the patient appeared to have a frequent HLA haplotype or in case of consanguinity or other interfamilial relationships, an extended family search was started simultaneously.[12] A haplotype can be defined as 'half of a genotype' of which all genes are located on the same chromosome and are all inherited from one parent. In this study, 8.2 percent of the patients (n=38) had both an acceptable donor in the family as well

as an acceptable UD. In all of these cases the family donor was chosen. In the period 1987-1992 a 6 out of 6 or 5/6 matched donor (HLA-A, -B, -DR on split level by serology) was selected for both the adult and paediatric patients. Between 1992 until 1996 an 8/8 or 7/8 matched donor (HLA-A and –B on split level by serology and HLA-DRB1* and –DQB1* on allele level) was selected. From 1996 and onwards a 10/10 or 9/10 matched donor (HLA-A*, -B*, -C*, -DRB1*, -DQB1* on allele level) was selected. More mismatches were accepted in 13% of the patients for whom the search was started between 1996 and 2000. In all UD searches, a mixed lymphocyte culture was performed routinely and from 1992 onwards the cytotoxic T lymphocyte precursor assay was performed when possible. This was done to locate possible HLA mismatches that were not detected by serology, new alleles not detected by DNA typing and acceptable mismatches in case of mismatched donors.[13,14] The outcome of these assays was predominantly used to choose the best donor among a group of donors and to determine whether or not to T cell deplete in case of paediatric patients. Patients were seldom excluded from transplantation because of the outcome of the CTLp assay. After this extensive histocompatibility testing, the most suitable donor was selected. Moreover, if possible a backup donor was selected, which was used in case the best donor failed to donate.[15] Next the work up of the chosen donor was started.

Data collection

The current data were collected from the donor search database and the archives of the patients' charts. The following variables, besides those mentioned in Tables 1a and 1b, were included in the study: date of registration at Europdonor, HLA phenotype, date and reason for ending the search, whether or not the patient was transplanted and the date of transplantation or cancellation. The diagnoses were categorized as high or standard-risk diseases. The following were classified as high-risk: an Acute Lymphocytic Leukaemia (ALL) or Acute Myelogeneous Leukaemia (AML) beyond first remission or in relapse; T-cell ALL and pro B-cell ALL; Chronic Myelogeneous Leukaemia (CML) in second chronic phase, accelerated phase or in blast phase; any malignancy that was by history unstable and unlikely to stay in remission; SAA, Fanconi Anaemia (FA), and Myelodysplastic Syndromes (MDS) with complications e.g. infections, bleeding and refractoriness to platelet transfusion.[5,9] We also analysed the searches (from 1996 until 2000) taking into account the urgency status given by the clinicians at the beginning of the search. The urgency status by the clinicians given to patients registered before 1996 was incomplete and therefore not analysed. Furthermore, we selected a group of patients with frequently occurring HLA phenotypes, arbitrarily defined as those patients who have 500 or more HLA-A, -B, -DR split matched donors in BMDW (file of 26-February-2002; 4.46 million donors) and analysed them separately. The cut-off point of 500 donors was chosen to ensure that the presence of an acceptable donor was no limiting factor for this group.

Statistics

All statistical analyses were executed in SPSS 11.0. The Chi-square test was used to analyse the distribution of variables. Binary logistic regression was used to check the relevance and calculate the odds of different variables on the search outcomes and transplantation. To compare the patient's age and search time spans, a T-test, or an one-way ANOVA together with a Bonferroni correction was used; the Mann-Whitney *U* test was used in case it was necessary to adjust for the smaller sample size. The competitive incidence analysis was used to plot the results on the search outcome against the time span. This analysis treats the different results of the donor search as mutually exclusive and exhaustive states events (i.e. a donor is found, no donor is found and deteriorated clinical condition before transplantation).[16] The Cox proportional hazards test was used to calculate its statistical significance.

Results

The patients

In both the paediatric and adult patient group there was an increase of patients over time (table 1a and 1b). Within the paediatric group there was no change in age distribution (p=N.S.), but within the adult group there was an increase of the median age of the patients (p=0.014). In the paediatric group there was a change in disease distribution between the second and third period (p=0.003). The most apparent was the increase of the percentage of patients with ALL in the third period. The percentage of paediatric patients of non-Northwest European origin increased significantly due to the increased number of patients referred to us with inborn errors (p=0.005). In the adult group there was no difference in disease distribution (p=N.S.). In both, the paediatric and adult group, there were no significant changes in the proportions of the disease risk categories. The sex ratio of the paediatric patients was 50/50 in the first period (p=N.S.) but in the last two periods there were more male patients than female ones (in both cases p=0.001). In the adult group there were more male patients within the first period (p= 0.003). In the second and third period, this difference from the 50/50 sex ratio was no longer significant (p=N.S.).

Table 1a: The characteristics of the 275 paediatric patients for whom a UD search was activated.

	Period of search activation			
	1987-1990	**1991-1995**	**1996-2000**	**Total**
Number of patients	n=36	n=101	n=138	n=275
Characteristics				
Sex (male/female)	20/16	67/34	89/49	176/99
deviation from 50/50 ratio*	p=N.S.	p=0.001	p=0.001	
Age median (range) †	6.4 (0.4 - 15.7)	5.5 (0.3 -15.6)	6.5 (0.1 - 15.9)	6.0 (0.1 - 15.9)
N.W. European /non-N.W. European origin	34/2	84/17	99/39	217/58
Diagnosis n (%) !				
ALL	5 (14%)	14 (14%)	45 (33%)	64 (23%)
AML	8 (22%)	12 (12%)	14 (10%)	34 (12%)
CML	3 (8%)	9 (8%)	4 (3%)	16 (6%)
MDS	2 (6%)	14 (14%)	16 (12%)	32 (12%)
Lymphoma	-	2 (2%)	1 (1%)	3 (1%)
Other malignancies	3 (8%)	1 (1%)	10 (7%)	14 (5%)
SAA	6 (17%)	15 (15%)	13 (9%)	34 (12%)
Immune deficiencies	4 (11%)	17 (17%)	11 (8%)	32 (12%)
Other non malignant diseases	5 (14%)	17 (17%)	24 (17%)	46 (17%)
disease risk category:				
standard	10 (28%)	46 (46%)	51 (37%)	107 (39%)
high	26 (72%)	55 (54%)	87 (63%)	168 (61%)

*Deviation from the 50/50 sex ratio was calculated with the Chi-square test. †Difference in age was calculated with the ANOVA (p=N.S.). ‡Differences in disease distribution was calculated with the Chi-square test; between the first two periods (p=N.S.), between the second and third period (p=0.003).

Percentage of successful donor searches for patients of Northwest European origin.

The number of patients with one or more HLA-A, -B, -DR split identical donors in BMDW increased over time from 20% to 84%. This resulted in an increase of patients for whom a donor search ended in finding an acceptable donor from 37% to 69% (table 2). Within the first period the percentage of patients with a HLA-A, B, DR split matched donor in BMDW was lower than the percentage of successful searches, because at that period most donors in BMDW were still typed for HLA-A and B only. The probability to find an acceptable

Table 1b: The characteristics of the 273 adult patients for whom a UD search was activated.

	Period of search activation			
	1987-1990	**1991-1995**	**1996-2000**	**Total**
number of patients	n=59	n=84	n=130	n=273
characteristics				
Sex (male/female)	41/18	47/37	72/58	160/113
deviation from 50/50 ratio*	p=0.003	p=N.S.	p=N.S.	
Age, median (range) †	26.3 (16.2 - 49.7)	28.2 (16.1 - 52.1)	33.2 (16.4 - 53.6)	30.4 (16.1-53.6)
N.W. European / non-N.W. European origin	57/2	75/9	113/17	245/28
Diagnosis n (%) !				
ALL	14 (24%)	22 (26%)	32 (24%)	68 (25%)
AML	9 (15%)	18 (21%)	31 (24%)	58 (21%)
CML	19 (32%)	25 (30%)	35 (27%)	80 (29%)
MDS	5 (9%)	8 (10%)	12 (9%)	25 (9%)
Lymphoma	-	1 (1%)	9 (7%)	10 (4%)
Other malignancies	3 (5%)	1 (1%)	3 (2%)	7 (3%)
SAA	6 (10%)	6 (7%)	6 (5%)	18 (6%)
Other non malignant diseases	3 (5%)	3 (4%)	2 (2%)	8 (3%)
disease risk category ß:				
standard	23 (42%)	34 (40%)	50 (38%)	107 (40%)
high	32 (58%)	50 (60%)	79 (62%)	161 (60%)

*Deviation from the 50/50 sexratio was calculated with the Chi-square test. †Difference in age was calculated with the ANOVA (the median age of the patients has increased, p=0.014). ‡Difference in disease distribution was calculated with the Chi-square test (p=N.S.). §For 5 patients the disease state was unknown therefore transplantation urgency could not be established for these patients.

donor increased per period (Odds Ratio = 1.8; $p < 0.001$) and increased when a patient had a frequent phenotype (Odds Ratio = 2.5; $p = 0.003$). Other patient related variables, namely disease risk category, gender and age group did not influence the success rate of the UD searches (p = N.S.). Table 2 shows that the median time needed for a successful search in the third period was shorter than that in the first and second period ($p = 0.009$ and $p = 0.042$ respectively). There was no difference between the first and second period (p=N.S.).
Combining the median search time span with the search success rate in a cumulative incidence plot (Figure 1), displays the increasing efficiency of the search in time (Hazard Ratio = 1.7; $p < 0.001$). As expected, a higher probability to find an acceptable donor leads to a higher

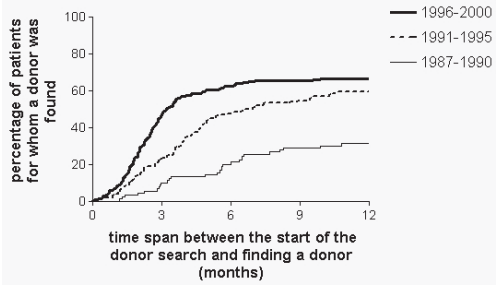


Figure 1: Cumulative incidence of patients of Northwest European origin for whom a donor was found within one year. *The Cumulative incidence increased per period (Hazard Ratio= 1.7; p < 0.001)*

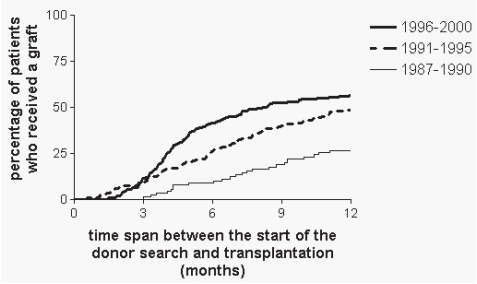


Figure 2: Cumulative incidence of patients of Northwest European origin that received a graft in one year after search start. *The cumulative incidence increased per period (Hazard Ratio= 1.5; p < 0.001)*

probability to transplant over time (Odds Ratio= 1.5; p = 0.001). The only other variable influencing the probability to transplant was having a frequent HLA phenotype (Odds ratio = 2.8; p < 0.001). However, it should be noted that not all patients with an acceptable donor were transplanted as some became medically unfit to proceed with transplantation. Between 1996 and 2000, 59% of the patients were transplanted within a median time span of 4.4 months (table 2) from the start of the search until the actual transplantation; as also shown in figure 2. The median time between the location of an acceptable donor and transplantation (2 months) however did not change throughout the whole period.

Table 2: The probability of finding a donor for patients of Northwest European origin; the probability of transplantation; the median time span in months from start of the search until an acceptable donor was found or until transplantation.

	Period of search activation			
	1987-1990	**1991-1995**	**1996-2000**	**total**
number of patients	n = 91	n = 159	n = 212	n = 462
Mean number of HLA-A, -B, -DR split typed donors in BMDW	23,071	325,174	1,330,807	
Donor search variables				
Potential HLA-A, -B, -DR split matched donors available in BMDW, n(%)	18 (20%)	97 (61%)	178 (84%)	293 (63%)
Donor accepted for transplantation, n(%)*	34 (37%)	99 (62%)	147 (69%)	280 (61%)
Search time span in months, median (range) †	5.6 (1.2-36.8)	3.9 (0.1-98.9)	2.5 (0.1-34.3)	2.9 (0.1-98.9)
Patients transplanted, n(%)	32 (35%)	87 (55%)	126 (59%)	245 (53%)
Deteriorated clinical condition, n(%)	28 (31%)	48 (30%)	63 (30%)	137 (30%)
Patients without a donor, n(%)	31 (34%)	24 (15%)	23 (11%)	78 (17%)
Time from start until transplantation in months, median (range) ‡	8.6 (3.0-105)	6.4 (0.6-69.8)	4.4 (1.5-33.0)	5.3 (0.6-105)
Time from start until withdrawl due to deteriorated clinical condition, median (range)	3.1 (0.2-133)	2.4 (0.2-91)	3.0 (0.1-53)	2.7 (0.1-133)

* The donor was chosen after histocompatibility testing. †Differences in the time span between the start of the search until an acceptable donor was found was calculated with the T-test: the time span of the searches performed between 1996 and 2000 are shorter than of those performed in the first and second period ($p = 0.009$ and $p = 0.042$ respectively); there is no difference between the first two periods (p=N. S.). ‡Differences in the time span between the start of the search until transplantation was calculated with the T-test: the time span of the searches performed in the periods 1991-1995 and 1996-2000 are shorter than of those performed in the first period ($p = 0.24$. and $p < 0.000$ respectively); there is no difference between the last two periods (p=N.S.).

Searches for patients with a frequently occurring HLA phenotype

In order to investigate whether the number of donors in BMDW was still a limiting factor for the UD searches started in the 1996-2000 time period, the search outcomes for patients with frequently occurring HLA phenotypes (i.e. 500 or more donors in BMDW; n=72) were analysed. For patients with such a frequently occurring phenotype a donor should be available, and failure to transplant could be attributed to search efficiency. In the period 1996-2000 74% of the patients with a frequently occurring phenotype were transplanted. The other 26% of the UD searches ended in the patients becoming medically unfit for transplantation before a donor could be located. There was no difference in time span between the searches for patients with a frequently or less frequently occurring phenotype (p=N.S).

Reasons for not achieving transplantation

Two main causes that lead to failure to reach transplantation were identified. [1)]Either no acceptable donor was available or [2)]the patients' clinical condition deteriorated to a point that stem cell transplantation was no longer an option (in these cases failure to find a donor was not the primary impediment). Failure to find an acceptable donor has decreased substantially over time (table 2). Between 1996 and 2000 this happened for only 11 percent of the patients.

In contrast, throughout 1987-2000 (table 2) 30% of the patients did not reach transplantation because of their deteriorated clinical condition, which could be caused by the search process being more time consuming because of difficulties to find a donor for a patient. But as stated before 26% of the patients with a frequently occurring phenotype also did not reach transplantation because of a deteriorated clinical condition. In addition, the median time span in which the patients were withdrawn from the search due to a deteriorated clinical condition was less than the median time needed for other patients to reach transplantation, as shown in table 2 (Mann-Whitney *U* test: 1987-1990: $p = 0.001$, 1991-1995: $p = 8 \cdot 10^{-6}$, 1996-2000: $p = 2 \cdot 10^{-4}$).

Tabel 3: Disease risk category and its impact on the percentage of Northwest European patients receiving a graft.

	Period of search activation			
	1987-1990	**1991-1995**	**1996-2000**	**total period**
Number of patients	n = 87	n = 159	n = 211	n = 457
Donor search variables				
High risk patients	n = 55	n = 90	n = 131	n = 276
Deteriorated clinical condition, n (%)	16 (29%)	32 (36%)	47 (36%)	95 (35%)
Patients transplanted, n (%)	20 (36%)	47 (52%)	72 (55%)	139 (50%)
No donor found, n (%)	19 (35%)	11 (12%)	12 (9%)	42 (15%)
Standard risk patients	n = 32	n = 69	n = 80	n = 181
Deteriorated clinical condition, n (%)	10 (31%)	16 (23%)	15 (19%)	41 (23%)
Patients transplanted, n (%)	12 (38%)	40 (58%)	54 (67%)	106 (58%)
No donor found, n (%)	10 (31%)	13 (19%)	11 (14%)	34 (19%)

Another possible cause for not reaching transplantation because of a deteriorated clinical condition is that the patient already has an advanced disease state at the start of the search. High-risk patients did have a 2.3 higher odds to become medically unfit for transplantation between 1996 and 2000 (table 3, p = 0.012). This however did not result in a significant difference in the chance of receiving a graft (p = N.S.). The gender and age of the patient also did not influence the occurrence of deteriorated clinical condition. From 1996 until 2000 the clinicians indicated high and standard transplant urgency on the basis of their clinical assessment at the start of all donor searches. The median time span between the start of the search and transplantation for these high-urgency searches was 3.9 months compared to 4.9 months for standard-urgency searches (Mann-Whitney *U* test, p=0.004). There was neither a difference in the percentage of patients transplanted, nor in the failure to transplant due to a deteriorated clinical condition (data not shown, p = N.S).

The time span of the donor search process

In order to identify the bottleneck of the search process, we measured the median time spans of the most essential parts of the searches performed between 1996 and 2000. The median time span between the identification of a patient as a candidate for an active unrelated donor search and receipt of the patient's blood for histocompatibility testing was 8 days (1 – 149 days). The median time span between requesting and receiving donor blood was 14 days (1 – 286 days). The median time between receiving the blood of the last requested donor and

choosing a donor for transplantation was 26 days (1 – 193 days). The time between choosing a donor after histocompatibility testing, and starting the work up of the donor was 5 days (1 – 421 days) and the median time between the start of the work up and transplantation was 52 days (1 – 218 days).

Patients of non-Northwest European origin

In table 4 we can see that the search success for these patients was consistently less than for those of Northwest European origin. In the period 1996-2000 for only 36% of these patients an acceptable donor was found, despite the increase of the percentage of patients with a HLA-A, -B, and -DR split donor in BMDW to 59% (p=0.04); 32% of the patients were transplanted in the same period.

Table 4: The probability of finding a donor for patients of non-Northwest European origin; the probability of transplantation; the median time span in months from start of the search until an acceptable donor was found or until transplantation.

	Period of search activation			
	1987-1990	**1991-1995**	**1996-2000**	**total**
Number of patients	n = 4	n = 26	n = 56	n = 86
Donor search variables				
Potential HLA-A, -B, -DR split matched donors available in BMDW, n (%)	0 (0)	9 (35%)	33 (59%)	42 (49%)
Donor accepted for transplantation, n(%)*	0 (0%)	8 (31%)	20 (36%)	28 (33%)
Median time span until donor found in months (range)	-	2.6 (0.4-30.9)	2.1 (0.7-6.3)	2.2 (0.4-30.9)
Patients receiving a graft, n (%)	0 (0%)	6 (23%)	18 (32%)	24 (28%)
Deteriorated clinical condition, n (%)	1 (25%)	3 (12%)	10 (18%)	14 (16%)
No donor can be found, n (%)	3 (75%)	17 (65%)	28 (50%)	48 (56%)
Median time span until transplantation in months, (range)	-	8.5 (2.3-33.3)	5.0 (2.3-12.5)	5.0 (2.3-33.3)

*: The donor was chosen after histocompatibility testing.

Discussion

The searches for acceptable unrelated haematopoietic stem cell donors for Northwest European patients have become more successful over time. Due to the increased worldwide donor pool, the percentage of patients transplanted was almost doubled in the described time period. Additionally, the time spent on the search until transplantation was cut in half. During the period studied the sophistication and accuracy of HLA typing increased immensely and may have resulted in an increased stringency of HLA matching. This would have a negative impact on the search results, making it impossible to compare searches executed before and after 1996; when HLA allele typing became possible. However this did not affect our search outcome because cellular techniques were used routinely to detect many of the allele mismatches before HLA allele typing became possible. Retrospective analysis has shown the number of allele mismatches in the transplanted donor/patient couples were identical over the entire period of time (data not shown).

In spite of the improvements mentioned above and the possibility to transplant with a donor not perfectly matched for HLA, there were still patients for whom no acceptable donor was found, or who became medically unfit for an unrelated stem cell transplantation during the search process. Between 1996 and 2000 the absence of a donor was most frequent in searches for patients of non-Northwest European origin. These patients still have a lack of donors with the same genetic background in the worldwide file. The increase of HLA-A, -B, -DR split-matched donors in BMDW did not result in an increased search success for these patients, presumably because of the allele differences identified after high resolution HLA typing. Another factor could be the relatively high percentage of non-Northwest European donors not willing to proceed with donation.[17] In contrast only a small group of patients of Northwest European origin with rare HLA phenotypes could not be transplanted due to a lack of an acceptable donor. To be able to transplant this category of patients, the worldwide donor pool has to be increased. However, in the case of donors of Northwest European origin, the principle of 'diminishing returns' applies. Müller *et al.* calculated that adding an extra 100,000 donors to a registry of 1 million donors with a Northwest European background would only increase the chance on finding an HLA-A, -B, -DR split matched donor by 1%.[18] Nowadays BMDW includes over 3 million HLA-A, -B, -DR split donors, which makes the effect of adding 100,000 donors to the world wide donor pool even smaller. It may be more efficient to intensify the research on identifying acceptable mismatches, and to improve the transplant protocols using stem cells from HLA mismatched donors.[19-21] Contrary to the recruitment of Northwest European donors, the recruitment of new donors of non-Northwest European origin should be actively pursued, even though this has shown to be difficult. [7,10,22] Transplantation with cord blood units has shown to be successful for this group [23] as the matching criteria are less stringent. [24-28] Efforts to collect cord blood units from non-

Northwest Europeans should be encouraged. In spite of the increased search efficiency, the percentage of patients of Northwest European origin who became medically unfit to proceed with transplantation remained around 30% from 1987 to 2000. The percentage of patients becoming medically unfit did not depend on donor availability, as 26% of the patients with a frequent phenotype registered between 1996 and 2000 also became medically unfit for transplantation. Moreover the changes in the disease distribution, age, and sex ratio of the patients did not increase the proportion of high-risk patients. Therefore, the time span remains to be an important constraint on the UD search. This begs the question whether we can improve the effectiveness of the unrelated donor search further. One problem is to identify the patient group which is most likely to become medically unfit to proceed with transplantation. The urgency status as assessed by the clinicians failed to identify the majority of the patients with a rapidly declining clinical condition; the disease risk category on the other hand is too broad. As it seems difficult to predict which patients need a graft most urgently, it seems important to shorten the UD search time span until transplantation for every patient in need of a stem cell transplantation.

When looking at the time spans of certain parts of the search process we think there is room for improvement with regard to the speed of the search. The median time to receive a blood sample for histocompatibility testing of the patient and unrelated donors can and should be reduced. Using donors typed up front for HLA-A*, -B*, -C*, DRB1* and DQB1* alleles (high resolution DNA typing) could reduce the time to select a donor to less than three weeks. Standard allele level typing of all donors at the registries would require a major investment in order to develop low cost standardized high resolution HLA typing methods and to be able to handle the magnitude of the task; but it is probably more worthwhile than investing in the enlargement of the donor pool. Furthermore, in some cases an immediate transplant with a partially matched donor may be preferable to a prolonged search for a full match.[29]

Probably most could be gained from reducing the time span between the choice for a donor, and transplantation; taking in to account both the preparative regime for the patient and transplantation logistics. Precious time is lost on the waiting list of the transplant centres; ie. availability of ultra clean rooms or laminar air flows. In the most ideal situation a patient should be transplanted within three weeks after the donor has been identified, thus giving a time span of six weeks in total. Previous experience has shown that this is possible; own experience [30] and experiences of Susan Cleaver from the Anthony Nolan Trust (personal communication). However a prospective study is needed to verify whether the proposed reduction of the time span has the expected effect. A problem in this study was that the date on which the patient became medically unfit to be transplanted is not known. We know the date of search revocation, but that date is probably later in time giving an overestimation of the time span.

At present searches are conducted for patients whom did not yet reach the remission status. Patients, who never reach the remission status, are actively withdrawn from the search. Rapid donor searches could allow the clinicians to first finish the induction of remission before starting the UD search. This could decrease the amount of UD searches started in vain. Another argument in favour of a more rapid search is that with improved HLA matching the clinical results with UD compare favourably with that of HLA-identical sibling transplants.[19] However, in order to successfully use unrelated grafts for indications that are currently reserved for HLA-identical sibling transplants, it is essential that the UD searches should not take much longer than the preparation for a sibling transplant (6 weeks).
The present data suggests that the most efficient way to increase the percentage of patients of Northwest European origin reaching transplantation is to decrease the time spent on the whole process and to increase the level of HLA typing of the donors at the registries to allele level. Furthermore, we propose an enlargement of the availability of cord blood units from non-Northwest Europeans. These conclusions, based on actual data obtained from searches for Dutch patients, confirm the suggestions made by others [11,31-33] on UD searches for patients in the U.S. and in Europe, and therefore apply to UD searches for patients worldwide.

Acknowledgements

We would like to thank D. L. Roelen PhD, G. M. Th. Schreuder PhD and Prof. A. Brand MD PhD for their constructive comments on this manuscript and E. J. M. A. van Hoof MA for his editorial corrections on the English language.

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