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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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3

The importance of identifying a back-up donor for unrelated stem cell transplantation

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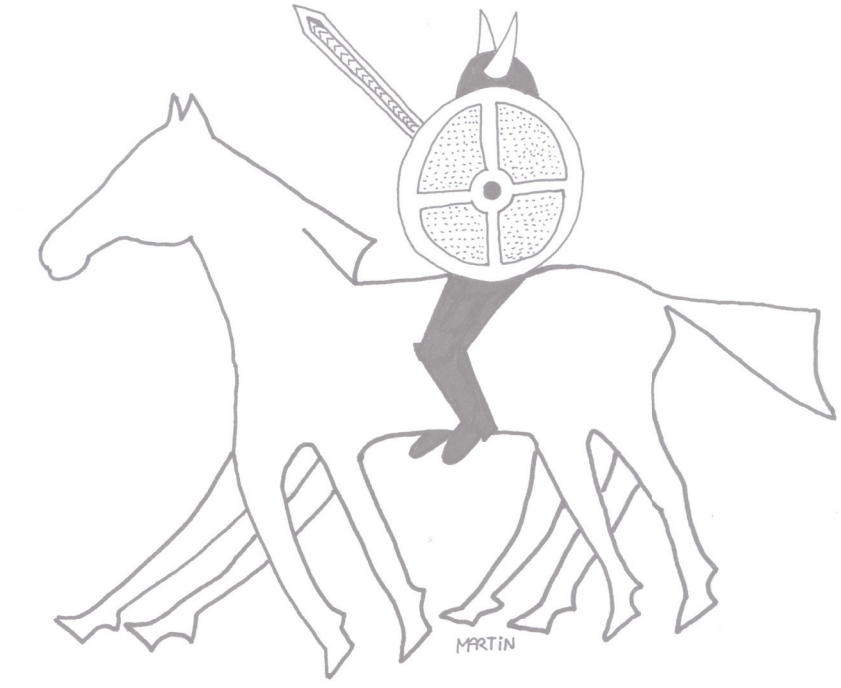

Odin and his horse Sleipnir

Abstract

The importance of identifying a back-up donor, once a primary suitable unrelated stem cell donor has been found is often underestimated. Transplant centres erroneously count on the unrelated volunteer donors to be willing, available, and medical fit for actual donation. According to our data, which includes 502 unrelated donor work up procedures performed for 425 Dutch patients between 1987 and 2002, one out of eleven work ups ended in the primary requested donor failing to donate. Of all donor related cancellations (N=46), 78% of the procedures were deferred due to medical reasons and 22% due to non-medical reasons. Most of the donors deferred for medical reasons were female (p=0.005). In 50% of the cases for which a back-up donor was already identified, the patients were transplanted with a delay of less then two weeks; when no back-up donor was available, the median delay increased to 18 weeks.

We strongly encourage implementing a search for at least one back-up donor in the primary search. Identifying a back-up donor can save precious time and complicated logistic rescheduling.

Introduction

Approximately one out of three patients in need of stem cell transplantation has a suitable related donor[1]. The remaining patients depend on allogeneic transplantation with stem cells from an unrelated but Human Leukocyte Antigen (HLA) compatible donor, as this has proven to be a suitable alternative[2]. Europdonor facilitates unrelated stem cell donor searches for Dutch patients since 1987. Improving qualities of international services like Bone Marrow Donors Worldwide (BMDW) has shortened the search period over the past years. The confrontation with the deferral of the chosen donor, just prior to the transplantation procedure has lead to a search policy in which we try to identify two donors for each patient. The best donor is chosen, the second best donor is released as a back-up donor. Studies performed on the availability of unrelated donors during confirmatory HLA typing stage have shown the relationship between psychological factors concerning volunteer history, recruitment and donation and the level of attrition[3-4]. Deferral of a chosen donor prior to harvest is less than optimal; without an identified back-up donor, a new search has to be performed which is time consuming and can lead to necessary extra treatment courses and hospital admissions for the patient. Until now no data has been available on the advantage of identifying a back-up donor in the first search for a patient. It is our policy to identify a stem cell donor and back-up donor for each patient whenever possible. We addressed the question whether a back-up donor saves precious time and analysed the different reasons for not completing a donor work up procedure, with special attention given to the donors' deferral.

Materials and methods

The analysis concerned the 502 work up procedures following unrelated donor searches for 425 Dutch patients facilitated by the Europdonor Foundation in the Netherlands, from 1987 to 2002. Patients originated from the following transplant centres: the Leiden University Medical Centre (n=204, 71 adults/133 children), Erasmus Medical Centre/Daniel Rotterdam (n=108) and the University Medical Centre Utrecht (n=113, 84 adults/29 children). Statistical analysis was performed in SPSS11 using Chi-square test and Mann-Whitney U test.

Our search criteria include HLA match grade, CMV status, donor gender, donor age, and ABO blood group system[1]. Confirmatory HLA typing and additional immunogenetic testing, such as Mixed Lymphocyte Culture (MLC) and Cytoxic Lymphocyte precursor test (CTLp) are performed with potential donors and the best-matched donor is requested for work up. A work up procedure involves the formal request for physical examination and preparation of a donor for stem cell harvest. The transplant centre can express the preference for bone marrow or stimulated peripheral blood stem cells with the decision being driven largely by the patient condition and disease stage, or current transplant protocol. It depends on the policy of the donor registry and the willingness of the donor to determine if this request can and will be fulfilled. The transplant centre determines a tentative date for transplantation. The donor centre contacts the chosen donor for counselling and physical examination, and arranges the definitive date for the stem cell harvest. At time of the work up request of the best-matched donor, the second best donor is selected to be the back-up donor in case the first donor fails to donate. This donor is released with the remaining donors, informing the donor registry that he/she is the back-up donor. The determination to release this back up donor to the world-wide donor pool is based on the policies of each individual donor registry; ranging from immediate release to a temporary removal from the donor pool to await the outcome of the primary donor's evaluation and consent.

Results

Between 1987 and 2002, 502 work up procedures with unrelated stem cell donors for 425 Dutch patients were initiated. Overall 120 work up procedures were cancelled. In total 359 first transplantations, twenty-one second transplantations and two third transplantations were performed. In thirty-six of the first transplantations and eleven of the second transplantations, a back-up donor was asked to donate stem cells. The reason to request the back-up donor at time of second transplantation was deferral of the first donor in one case and preference of the transplant centre in the other cases. In total 492 donors were involved, 265 males, 218 females; of nine donors the gender was not reported.

Cancellations

In 15% (74/502), the work up procedure was cancelled due to patient related reasons, primarily because the patient was no longer eligible for transplantation. In 9% (46/502) the donor was deferred. Table 1 shows the grounds for donor deferral. They were either personal (n=10, five male and five female donors) or medical (n=36, 11 male and 25 female donors). The proportion of female donors in the latter group is higher than in the group of all requested donors (p=0.020). Reasons for donors' medical deferral were in a number of cases specified by the donor centre, although they have no obligation to do so. Female donors have an increased rate of deferral for medical reasons compared to male donors (p=0.005). In this study pregnancy is considered a medical reason for unavailability, with regards to international regulations for donor eligibility.

Table 1. Reasons for donor cancellation at time of work up

Reasons for cancellation	specifications	male	female
non medical, n=10 *		5	5
	unavailable	2	
	no longer interested	2	4
	unspecified	1	1
medical, n=36 *		11	25
	obesity	1	2
	pregnancy		5
	malignancy		2
	infectious disease	2	2
	liver/kidney/thyroid failure	1	2
	vascular	1	1
	multiple sclerosis		1
	M. Willebrand	1	
	unspecified	5	10
total		16	30

*Female donors are deferred more often, due to medical reasons:
Chi-square test: p=0.005

Back-up donor

Confrontation with donor deferral during the work up stage has led to our current policy to attempt to identify a donor and a back-up donor for each patient. Overall, in 63% (305/502) of all examined work up procedures, a potential back-up donor was identified in the initial donor search. The number of patients for whom a back-up donor was identified has improved during the past years. In the first years (1987-1989), a back-up donor was found for only 28% of the patients. In the last three years (1999-2001) a back-up donor was identified for 66% of all patients. Currently, 81% of our unrelated donor searches result in the identification of a back-up donor (table 2). In these cases all other donors tested had too many mismatches to be acceptable.

Table 2: Improvement of back-up donor identification over time

period in time	patients with a backup donor / work ups	(%)
1987-1989	6 / 21	(29%)
1999-2001	121 / 183	(66%)
2002-2004*	214 / 265	(81%)

* the work up procedures until the June 30, 2004 are included
Chi-square test: $p= 2.10^{-7}$

In 46 of all cases the best donor was deferred after the formal request for physical examination and preparation for stem cell harvest. For 10 patients an unrelated stem cell donor search had to be re-opened. In 36 of the 46 cancelled work up procedures a back-up donor had previously been identified. In 35 of these cases the back-up donor was requested to donate stem cells. Twenty-nine patients were transplanted with this back-up donor, mostly without major delay. For one patient stem cell transplantation was no longer an option. Five of the requested back-up donors were not eligible for stem cell donation due to medical reasons.
The absence of a back-up donor can cause delay or even cancellation of the preferred therapy. The regular time delay in a work up procedure is defined as the difference in days between the tentative date for transplantation at time of the work up request and the final transplantation date. The transplant centre proposes the tentative date for transplantation; depending on the availability of both the donor and the collection centre, the final date for collection will be determined in consultation with the transplant centre. The median delay of patients transplanted with the best donor is 0 days (range 0-155). Over 85% of the first

transplantations took place within a period of less then 14 days from the tentative date. To investigate the delay caused by the deferral of a donor during the work up procedure, we determined the difference in the first tentative harvest date and final harvest date. In 29 patients, transplanted with a back-up donor a median delay of 7 days (range 1-100 days) occurred.
In 10 cancelled work up procedures no back-up donor had been identified and a new unrelated donor search had to be started. Six patients were transplanted with a median delay of 129 days (range 40-555 days). The other four patients were no longer eligible for transplantation. An overview of the advantage in time of an initially identified backup donor is given in Table 3.

Table 3. The advantage in time of an initially identified back-up donor. The delay is defined as the difference between tentative and final harvest date.

	median delay	range	% transplanted
best donor available (n= 371)	0 days	0-155 days	87%
best donor deferred: back-up donor available (n=36)	7 days	1-100 days	63%
best donor deferred: no back-up donor available (n=10)	129 days	40-555 days	60%

Discussion

A successful unrelated donor search does not guarantee the availability of the identified donor for stem cell harvest. During the initial search, HLA typing and additional laboratory tests are performed. The best donor is chosen and requested for stem cell donation; the second best or so-called back-up donor is released. It is our experience that more patients are now referred to us for an urgent search, with an initial proposed time frame for transplantation within 6 to 12 weeks. This is likely a result of our success in being able to locate donors in a very short notice[5-6], and changes in current transplantation practice. A variation between 0-14 days in the proposed and final harvest date is considered acceptable. The policy to structurally identify a back-up donor was introduced in 1994 in our search process. Since then, the total number of identified back-up donors for Dutch patients has tripled over the years. This could be attributed to the increasing number of registered donors worldwide[7] in combination with our evidence based search strategy.

In 46 cases the donor centre cancelled the work up procedure. The reasons for donor cancellation were divided in medical and non-medical reasons. A significant number of female donors were deferred due to medical reasons (p=0.005). The preference for the selection of male donors for stem cell transplantation was discussed before in relationship to transplant-related mortality, relapse incidence, and Graft versus Host Disease[8-11]. On the basis of our findings and facts as described in the literature, the transplant centres prefer male to female donors if possible.

The reasons for a medical cancellation are not always specified, although, a donor centre is free to give information to the transplant centre in this point. In a number of cases the medical reason was specified. Obesity is a major reason for donor deferral at donor work up stage, as a donor with serious obesity should be deferred at least at the time of confirmatory HLA typing request, but more favourably at the time of recruitment for the unrelated donor registry. Donor registries should give more attention to this point.

There was no difference in donor gender in the non-medical reasons. Being unavailable at the time of the work up request or personal withdrawal were the main reasons. Extensive education and information of the donor might reduce this number of cancellations. In terms of volunteer history it was found that stem cell donors who are also blood donors are less likely to drop out[3]. Generally, the transplant centre is not informed about the blood donor status of unrelated stem cell donors, therefore we could not confirm this finding.

To determine the benefit of identifying a back-up donor in the initial search, the degree of delay in a normal work up procedure has been established. A delay can be brought about by either donor related or patient related reasons. We showed that a delay caused by donor deferral could be minimised by identifying a back-up donor. The benefit of identifying a back-up donor not only results in more patients proceeding to transplantation, but also decreases the cost of overall treatment. This might be of substantial importance; a second unrelated donor search considers not only search costs, but also extra costs of needed treatment and hospital admission for the patient. Another aspect is the time that is needed to perform a second unrelated donor search. A number of patients will be at risk of relapse or deterioration of their disease, and will therefore no longer be eligible for stem cell transplantation if there is an untimely delay to transplantation due to donor deferral. It is yet unknown how the search procedure affects the mental state of health of the patient. It is recommended for future search to investigate in experiences of patients who are enrolled in an unrelated stem cell donor search, especially when arrangements for transplantation are made (e.g. patient's conditioning regimen is started), and the transplantation is deferred due to a donor cancellation and no back-up donor is available.

Conclusion and recommendations

Donor deferral, in particular during the work up procedure, is never welcome and can cause a serious delay. It is strongly advised to donor registries to ask for basic medical information (including height and weight) at the time of recruitment, and certainly at the time of confirmatory HLA typing request, to prevent unwanted surprises. Our search strategy, including the search for a back-up donor, prevents unnecessary loss of precious time for both patient and transplant centre. With the knowledge of almost 10% donor cancellations during the work up procedure, identifying a back-up donor should be a standard element in the search process. It is therefore strongly advised to identify a back-up donor in the initial search and to inform the donor centre about the back-up donor status at the time a donor is released. On the basis of these results transplant physicians are now better able to inform the patient concerning the possible obstacles in the unrelated search and donor work up procedure. The information should include a discussion of the likelihood that the identified suitable donor may not precede to actual donation.

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