Cord blood stem cells for hematopoietic stem cell transplantation in the UK: how big should the bank be?

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ABSTRACT

Background
A stored cord blood donation may be a valuable source of hemopoietic stem cells for allogeneic transplantation when a matched sibling donor is not available. We carried out a study to define the optimal size of a national cord blood bank for the UK.

Design and Methods
We calculated the actual numbers of possible donors and the chance of finding at least one donor for 2,000 unselected and for 722 non-North Western European patients for whom searches had been initiated as a function of three levels of HLA matching (4, 5 and 6 out of 6 alleles by HLA-A, -B low and -DRB1 high resolution HLA typing) according to various donor bank sizes.

Results
With a bank size of 50,000, 80% of patients will have at least one donor unit available at the 5 out of 6 HLA allele match level (median 9 donors per patient), and 98% will have at least one donor at the 4 out of 6 allele match level (median 261). Doubling the size of the bank yields at least one donor for only an additional 6% of patients at the 5 of 6 allele match level. Moreover, for non-North Western European patients a 50,000 unit bank provides a donor for 50% at the 5 allele match level, and for 96% at the 4 allele match level.

Conclusions
A bank containing 50,000 units is optimal for the UK and larger banks would only marginally increase the chance of finding suitable units.

Key words: cord blood, banking, stem cell transplantation.

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Introduction

Cord blood is a widely accepted source of progenitors for hemopoietic stem cell transplantation (HSCT)[1-3] and more than 10,000 procedures have been performed worldwide.[4] The most important factors associated with outcome are the degree of HLA matching and the nucleated cell dose. A cord blood transplant can be performed with a 4 out of 6 HLA allele match (considering the HLA-A, -B, and -DRB1 genes), but ideally the unit should be matched for at least 5 out of 6 HLA alleles and should contain at least 2.5×10^7 nucleated cells (NC)/kg (recipient body weight). When these criteria are satisfied, therapy may be successful in more than 50% of patients.

More than 12,000,000 unrelated adult and cord blood units are available worldwide. However, the World Marrow Donor Association (WMDA)[4] reported that though there were 9,484 unrelated transplants performed worldwide in 2007, fewer than half of the 32,000 patients who require a transplant actually had a suitable donor. The failure to identify a donor is due to a combination of factors, including inability to identify a well matched donor, inability to locate a donor who does seem to match or a delay in a given donor's availability.[4,6] In 2007 in the UK a search for an unrelated donor was started for 1,260 patients, but only 40% actually received a transplant even with the contribution of 90 cord blood units (Anthony Nolan Trust annual report). At that time, UK registries had almost 650,000 donors[7] but 43% of UK patients still received transplants from overseas donors.[3,8] In the case of cord blood units, almost 80% of the donor units were imported. These data support the development of a large cord blood inventory in the UK.

Recently, the US Institute of Medicine at the request of the US Congress prepared a report that strongly encouraged cord blood banking for transplantation. The report stated that by increasing the size and quality of the existing cord blood inventory in the US, nearly 90% of patients who need a transplant should be able to find a suitable match from either cord blood banks or marrow donor registries.[9] The committee estimated that though there were already 50,000 units stored in national inventories at least 100,000 additional high quality cord blood units were needed. Most of this analysis was based on estimates of haplotype distribution for the US population.[10] A preliminary report presented by Rubinstein *et al.*[11] used an empirical analysis that compared actual patients and donors in their registry and obtained similar figures. This suggests that this practical exercise can be used to address the question of optimal inventory size.

In the UK, there is a public cord blood bank operated by the National Health Service Blood and Transplant Service (the NHS Cord Blood Bank) that currently holds 11,000 units and is aiming to accumulate 20,000 units in the next five years (*Watt S, personal communication*, Workshop on Developments in Cord Blood Collection for the UK Department of Health, 28th May 2008). To assess the real need for the UK we undertook an analysis using actual patients and donors with the aim of obtaining a more exact estimate of the number of cord blood units required to provide at least one donor for more than 95% of patients. First, to address the number of patients that can benefit, we performed a survey of the search activity and outcomes in a referral center in London with a large transplant practice and considerable ethnic diversity. Then, to calculate the size of such a program according to different degrees of HLA matching we used actual patients and volunteer unrelated donors listed in the Anthony Nolan Trust's register to do the simulation.

The lower stringency required for HLA matching when using cord blood as the source of hemopoietic stem cells (HSC) suggests that this therapy can be offered to most patients in need of a transplant, provided that a sufficiently large national bank containing high quality units can be established.[12] The key question addressed in this paper is how large the national inventory has to be in order to provide an acceptable donor for the majority of patients who could not otherwise receive a transplant.

Design and Methods

Survey at Kings College Hospital

We calculated the time that elapsed from the day when the decision was made to recommend an allograft to various landmarks in the patient's subsequent course. All patients for whom an unrelated search was started during 2005 and for whom an allogeneic transplant was the preferred therapeutic option (referred to as 'allo-mandatory') were eligible for the calculations. Sibling transplants performed during this period were taken as a control group. Patients were considered eligible for an unrelated donor search if there was no related donor matched for 5 or 6 HLA-A, -B, -DRB1 alleles. An eligible unrelated adult donor was defined as one matching for at least 9 out of 10 of HLA-A, -B, -C, -DRB1, and -DQB1 alleles defined by high-resolution typing. At this time, no cord blood program was active. To calculate time intervals in this study, day 0 (day of decision-to-treat) was the day when a patient and/or their corresponding sibling were bled for high resolution HLA typing. Thereafter we calculated the interval to various different events: the day when a formal unrelated search was actually requested, the day when an international search was requested, the day when an answer (either positive or negative) for all potential donors requested was received, and the day when the graft was actually infused. Frequencies were assessed using the final population of 60 formal unrelated searches performed for allo-mandatory indications. Times are shown using median and ranges and expressed in weeks from the day of decision-to-treat.

Analysis of the Anthony Nolan Register

The data used are from the Anthony Nolan Trust's *SOLAR* database. This database is hosted on Sun V440 server running Solaris 10 (Sun Microsystems Inc, Santa Clara, CA, USA) and Oracle 9.2 RDBMS (Oracle

Corporation, Redwood Shores, CA, USA). Programming for the compilation of these statistics was done using a number of Oracle SQL*Plus and PL/SQL scripts. Base scripts were run to extract and then incorporate the relevant data for the donor and patient pools into tables with structures more appropriate for the analyses we wanted to perform. These scripts selected information from the 'SOLAR' donor, patient and HLA tables, using 2 digit allele codes for the HLA-A and -B loci and 4 digit allele codes for the HLA-DRB1 locus. HLA-DRB1 codes specified by the National Marrow Donor Program (NMDP) were converted to 4 digit codes using a probability table (only donors/patients where the 4 digit code was deemed to have a probability of 95% or greater of being correct for that particular NMDP code were included in the pools). One script selected information on all suitable *active* patients only (first simulation for overall population) and a second script selected information on all suitable patients (active and closed) where the ethnicity was known but not specified as North Western European (second simulation for patients with non-North Western European origin). As a result 2,000 consecutive active patients were selected (first simulation) for analysis, and the ethnic group breakdowns for the 722 non-North Western European patients used is shown in Table 1.

Following completion of the script, each of the two base scripts was run to produce the statistics. The match probability statistics were generated by successively running a SQL query for each donor sample size. This was a nested query. The inner query calculated the best overall match level (number of matching HLA-A, -B and -DRB1 values between individual donors and patient) for each patient with respect to the sample set of donors. The outer query calculated the percentage of patients that achieved each of the match levels (4 of 6, 5 of 6 and 6 of 6 alleles). To determine the median number of donors per patient (as a measure of redundant units in the panel) the calculation was generated by scanning the table for each match level ordered by the number of matched donors and the value was extracted where half of the patients were lower and half higher. The statistical results were entered into Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) to produce the charts.

Table 1. Ethnic background of 722 patients registered with a known non-North Western European origin.

Origin	Count	Percentage
African	71	9.83
African-Caribbean	57	7.89
Asian	231	31.99
Eastern European	26	3.60
Hispanic	16	2.22
Jewish	11	1.52
Mediterranean	97	13.43
Middle Eastern	108	14.96
Oriental	35	4.85
Other	70	9.70
Total	722	99.99

Results

Survey of patients requiring an unrelated donor at Kings College Hospital during 2005

During this period 104 patients were considered for an allogeneic transplant (24 sibling and 80 unrelated) but only 73 were considered allo-mandatory. Of these, 13 underwent a transplant from a sibling donor and for 60 a search of the UK donor registries was initiated (Figure 1). Median time from formal search to availability of a donor was 11 weeks (6-45). If the international registries were searched (because there was no UK donor), this time was increased by three weeks (0-4). Once the donor was confirmed and judged medically fit to donate, the transplant center needed an additional ten weeks (2-24) to proceed with the transplant. The overall time from the intention-to-treat to the actual transplant was 26 (11-49) and 29 (12-56) weeks depending on whether the patient received a UK or a non-UK donor. This figure resulted in a delay of 7-10 weeks compared to the 13 allo-mandatory sibling transplants performed during the same period. Importantly, the median time to define a search failure was estimated at 28 (2-68) weeks. Overall, 38% of the patients found a donor within a UK register and 33% from registers overseas. In this cohort, 28% of the patients failed to find a donor. Moreover, 20 patients (33%) that found a donor were not transplanted due to disease progression or deterioration in medical status. Consequently, only 38% of patients initially requesting unrelated donors were finally transplanted.

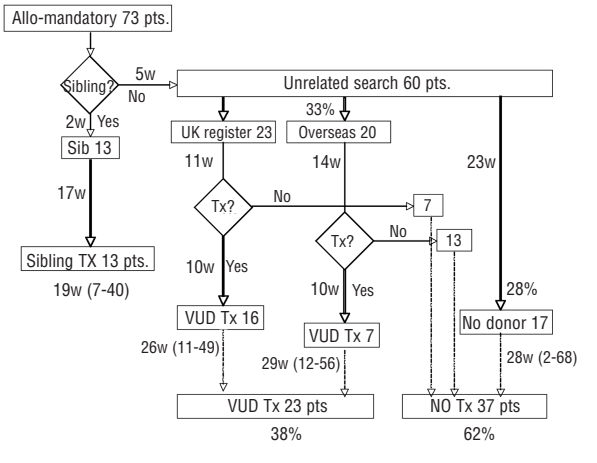

Figure 1. Flowchart on the outcome of patients requiring allogeneic hemopoietic stem cell transplantation at Kings College Hospital during 2005. During this period 104 candidates for allogeneic transplantation were identified. Eleven sibling transplants were considered second line therapy and 20 unrelated searches were withdrawn after the original request. The survey analyses outcome after intention-to-treat of 73 patients whose allogeneic transplantation was their first option (allo-mandatory). Time is expressed in median weeks (range). Figures in the boxes represent the actual number of patients reaching each stage and the percentage from the starting 60 patients requesting an unrelated donor.

Probability of finding at least one donor according to match categories

In order to define the size of a cord blood register, we looked at two different scenarios: (i) we selected the HLA genotypes of a cohort of 2,000 patients recently submitted to the Anthony Nolan Trust where the HLA typing included HLA-A, -B loci by low resolution (two digit) and HLA-DRB1 by high resolution (four digit). The size of donor registry was predefined by selecting a consecutive number of extracted donors to complete 1, 100, 1,000, 10,000, 50,000, 100,000 and 150,000. Figure 2 shows the probability of finding at least one donor for each match category for the various different registry sizes. The study showed that 50,000 donors would be required to provide at least one donor for 98% of the patients with at least a 4 out of 6 HLA match, to 80% with a 5 out of 6 match, and to 34% with a 6 out of 6 match. The median number of donors per patient in each of these categories was 261, 9 and 0, respectively. This also showed that increasing the cord blood bank size to 100,000 had a relatively small impact on the probability of finding donors, 1%, 6% and 7% increases in the 4, 5 and 6 out of 6 categories, while increasing the bank size increases substantially the redundancy within the registry (103%, 111% and 0% for each match category, respectively) (Table 2).

(ii) From the complete list of all suitable patients, we selected those with a known ethnic origin other than North-Western European. Figure 3 shows the same analysis as described above but exploring the registry size for 722 patients with a non-North Western European background. For this selected patient group the results showed that a registry of 150,000 donors, three times larger, would be required to provide at least one donor to 99% of the patients with at least a 4 out of 6 HLA match, to 77% for a 5 out of 6, and 17% for a 6 out of 6 match. However, the median number of donors per patient in each of these categories was still lower (121, 3 and 0, respectively). Table 2 shows the result for 50,000 donors and the improvement achieved by doubling the registry size. In this case, doubling the bank size to 100,000 units would increase the probability of finding a donor by 3%, 14% and 4%, respectively.

Discussion

Allogeneic HSCT is the preferred treatment for a wide variety of disorders but relies on the presence of an appropriate donor. Currently, in the absence of a sibling donor, for a patient for whom an allogeneic procedure is mandatory, an HLA matched unrelated volunteer donor (optimally matched for a minimum of 9 out of 10 high resolution HLA alleles) is the treatment of choice. In order to understand the impact of a cord blood transplant programm for the UK, we analyzed the search activity in a large bone marrow program in an experienced center with high ethnic diversity. Only adult donors were searched at this time since no cord blood

Table 2. Comparison of the efficiency of a cord blood inventory of 50,000 *vs.* 100,000 units: percentage of patients finding at least one donor and median number of donor found in each category.

Match level	% 4 out of 6 or better		% 5 out of 6 or better		% 6 out of 6	
Donor size	50,000	100,000	50,000	100,000	50,000	100,000
2,000 active patients	98.5% (261)*	99.6% (532)	79.5% (9)	85.6% (19)	34.1% (0)	41.4% (0)
722 non-North Western European patients	96.6% (35)	99.7% (68)	49.7% (0)	63.3% (1)	8.9% (0)	13.0% (0)

**Figures in parentheses express the median number of donors found for the total of patients in each group.*

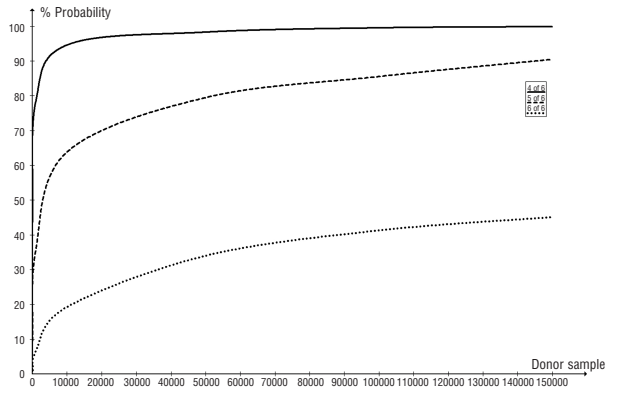

Figure 2. The probability of finding at least one donor 4, 5 or 6 out 6 HLA A, B by low and DRB1 by high resolution according to different inventory size for 2,000 consecutive patients requesting stem cell grafts recently at the Anthony Nolan Trust. Curves were calculated after assessing percentage of patients finding at least one donor for each predefined donor size (1, 10, 100, 1,000, 10,000, 50,000, 100,000 and 150,000) selected from those listed having a known DRB1 high resolution typing.

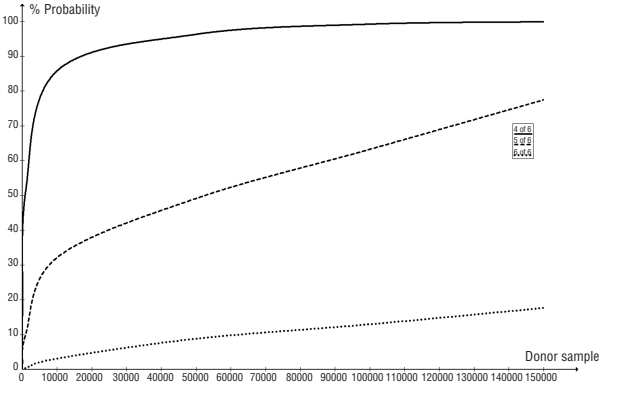

Figure 3. The probability of finding at least one donor 4, 5 or 6 out 6 HLA A, B by low and DRB1 by high resolution according to different inventory size for 2,000 consecutive patients with a known non-North Western Europe origin and high resolution DRB1 typing. Curves were calculated after assessing the percentage of patients finding a donor for each predefined donor registry size (1, 10, 100, 1,000, 10,000, 50,000, 100,000 and 150,000) selected from those listed with a known DRB1 high resolution typing.

program was in place. The results showed that 28% of searches failed to find a donor and only 38% of the searches initiated actually resulted in transplantation with a two-month delay compared to sibling allografts. Other registries showed similar results. Data from adult bone marrow registers clearly show the need for a complementary adult/cord blood donor program. For example, the German registry published the rate of success for their patients according to time; about two months were required to find a donor for half of their patients, and after four additional months close to 80% of patients finally found a donor, leaving 20% with no donor.[13] Recently, Dew *et al*.[14] published NMDP data from the US showing that the probability of no match was 8% for a North-American population of European descent and between 11% to 38% for other ethnicities. It is worth emphasizing that there is a size for a donor registry beyond which adding extra donors is no longer cost-effective.[15]

Establishing a cord blood program can reduce the proportion of patients for whom no donor is found. Importantly, using a combined adult donor and cord blood search, fewer than 5% of patients would have failed to find a match in our Kings College Hospital study. If then one considers transplant activity for 2006 (496 unrelated transplants) summarized by the British Society for Blood and Marrow Transplantation (BSBMT) the data would suggest that up to 100 additional patients could be transplanted in the UK with a cord donor. This combined search of donor registries and a cord bank of appropriate size would increase the access to transplantation and reduce the time from decision-to-treat to the actual transplant.

Our data define the size for a UK National Cord Blood Bank based on the probability of finding at least one HLA matched donor for each patient. The calculation used HLA phenotypes of actual patients and actual adult donors listed in the register. Ethnical composition of donor and recipient pools were similar reflecting the expected population published by the UK 2001 Census. The ideal size appeared to be around 50,000 units. Using the Anthony Nolan Trust register, this size allows identification of at least one 5 out of 6 HLA matched donor for up to 80% of the patients. Moreover, the median number of donors found per patient matched is 9, increasing the probability of finding at least one donor at an optimal cell dose. Larger banks would only marginally increase the chance of finding suitable units, and as reported, would substantially raise the cost per life-year gained.[16]

If we accept that 50,000 units is the optimal size of the bank, the next question is what is the minimum number of cells required to make storage of a given unit cost-effective. Using data provided by the Programa Sang de Cordó in Barcelona and illustrated in Table 3, the minimal pre-freezing cell number, based on storage efficiency and cost, seems to be 9×10^8 total NC. Using this cut-off a bank might need to discard 45% of units collected, while providing 5 out of 6 matched cords for 70% of patients weighing more than 50 Kg. This would cost €1,120 per stored unit. Even the cut-off of 9×10^8 might in fact prove to be too low if enough large banks containing cord units with many more cells per unit were established worldwide, because cord units with relatively low cell numbers, even though they were above the designated threshold, might not be selected.

In this analysis, we have also addressed the question of patients other than those with a North Western European background. According to these results a cord blood bank should contain at least 150,000 donors to achieve the same chance of finding a matched donor as in an unselected population. Nevertheless, a bank of 50,000 units will still find donors for 49% at 5 out of 6 match category. Furthermore, we think that a cord blood program orientated to recruit ethnic minorities would increase the chance of finding donors for such patients. In this regard, the Anthony Nolan Cord Blood Bank started to collect cord cells at Kings College Hospital Maternity Unit because the population is highly diverse and 68% of deliveries are from mothers of a non-North Western European background.

In general terms it would be desirable for each country to develop its own cord blood program, since this would increase the diversity of available donor units. The advantage for each country would be that using their own resources a substantial proportion of their population could be covered by their own donors with a reasonable investment. Moreover, international co-operation could guarantee universal access to therapy for practically all patients in need. To make it possible, international standards and accreditation processes are mandatory since quality is paramount for the success of this stem cell modality.[17] Consequently, we support proposals from Netcord-FACT for a rigorous international accreditation system for cord blood banking.[18] Further studies are required to define the efficacy of a global inventory including the units from all banks accredited at the international level. Furthermore, if appropriately stored, cord blood units may remain viable for many years or even decades[19] and could become a valuable resource for possible future clinical techniques that require stem cells or lymphocytes.

In conclusion, given the increased need for stem cells

Table 3. Cost benefit analysis for a bank targeting 50,000 units according to different minimum numbers of cells in stored units.[1]

Pre-freezing minimum cut-off ($\times 10^8$ nucleated cells)	5	9	12.5
Recipient bodyweight[2]	38 kg	55 kg	64 kg
5 out of 6 > 50 kg*	40-70 (0-4)	44-75 (0-6)	49-80 (0-9)
Discarded units	14%	45%	62%
Cost/unit+	€920	€1,120	€1,360

*[1]Cellular data provided by Programa Sang de Cordó. [2]Recipient's bodyweight (median) is calculated by dividing median number of cells expected in each cut-off by 2.5×10^7 (the minimal cell dose per kg suggested as optimal). *Minimum range is the probability of finding at least one donor for non-North Western Europeans and maximum range for the unselected patients considering only units suitable for patients larger than 50 kg. Figures in parentheses represent the median number of units found per patient matched respectively. The expected number of units with more than 2.5×10^7/kg for 50 kg is 22,000, 35,000 and 50,000 respectively. +Cost/unit is calculated by adding the cost of collecting, transporting and receiving 58,139, 90,909 and 131,579 samples and processing 50,000 respectively, according to the Anthony Nolan Cord Blood Bank.*

for transplantation from an ethnically diverse UK population those responsible for public health policy may need to review this issue. Here we show clearly that a national UK public cord blood bank should contain at least 50,000 high quality units and this could reasonably be achieved if the necessary funds were made available from a consortium comprising government (through the NHS cord blood bank) and various charitable institutions including the Anthony Nolan Trust. Cord blood banking complements the volunteer adult register and both should be independently efficient to make the allogeneic transplant a certainty. The availability of cord blood units that were not suitable for clinical use could be valuable for stem cell research and staff in cord blood banks could explore the possibility that specific components could be pooled for universal, non-personalized cell-based therapy.

Authorship and Disclocures

SQ, JAM: study design, data analysis and writing the manuscript; SGE, AML: study design and data analysis; GJM, JG: data collection and analysis; AP, BES, JMG: data analysis and writing the manuscript.

The authors reported no potential conflicts of interest.

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