Biology of Blood and Marrow Transplantation 8:257-266 (2002)

Searching for Unrelated Donor Hematopoietic Stem Cells: Availability and Speed of Umbilical Cord Blood versus Bone Marrow

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Received October 17, 2001; accepted February 4, 2002

ABSTRACT

Unrelated donor (URD) umbilical cord blood (UCB) has several potential advantages over URD BM for hematopoietic stem cell transplantation. To examine the efficiency of donor identification for each of these URD stem cell sources, we reviewed the search processes for all pediatric and adult URD transplantation referrals to the University of Minnesota during a period of 1 year. Of 171 consecutive referrals for URD transplantation, 108 patients proceeded to a formal URD search with selection of at least 1 donor. Significantly more formal UCB searches (54%) than BM searches (21%) were performed for patients who required urgent transplantation ($P < .01$). At least one 4-6/6 HLA-antigen matched UCB graft but no suitable BM graft was identified for 21 of the 108 patients (19%). The median time required to obtain a URD BM donor (from formal search to clearance of a BM donor) was 49 days (range, 32-293 days) compared to a UCB search time (from formal search to a donor unit chosen) of only 13.5 days (range, 2-387 days). For patients undergoing both BM and UCB searches, 29 more days (95% confidence interval, 21-37 days) were required to identify and clear a URD BM donor than a UCB donor ($P < .01$). For the 76 patients who proceeded to transplantation, patients receiving UCB received a transplant a median of 25 days more rapidly than did those receiving BM ($P < .01$). These data confirm that the availability of banked cryopreserved URD UCB grafts allows transplantations for patients with no available BM donor and that URD UCB grafts are available considerably faster than are URD BM grafts. Faster availability is a particular advantage for patients requiring urgent transplantation. These unique features of UCB transplantation must be considered in comparisons of the outcomes of UCB versus BM transplant recipients and in the design of prospective trials comparing URD sources.

KEY WORDS

Unrelated donor • Umbilical cord blood • Bone marrow • Transplantation

INTRODUCTION

Unrelated donor (URD) bone marrow transplantation (BMT) can be curative therapy in a variety of malignant and nonmalignant hematopoietic disorders [1]. However, many patients of non-European heritage do not have access to appropriately matched donors [2]. Umbilical cord blood (UCB) is being investigated as a new hematopoietic stem cell (HSC) source [3] and, unlike BM, has the advantage of absence of any risk to the donor. UCB transplantation (UCBT) has the potential to extend HSC transplantation to patients without HLA-compatible BM donors or to those in need of an immediate transplantation. In children, 0- to 3-antigen HLA-mismatch is tolerated without an increase in graft-versus-host disease (GVHD) or nonrelapse mortality [4], and UCBT is now being investigated in adults [5]. A further advantage of UCBT is the ability to obtain the UCB graft and proceed to transplantation more quickly. To investigate access to URD HSC, we reviewed our experience in terms of both success and speed of obtaining URD UCB and BM grafts for pediatric and adult patients during a 1-year period at the University of Minnesota.

METHODS

Patients and URD Grafts

All referrals for URD searches during 2000 were included in this analysis. Patients were eligible for URD transplantation

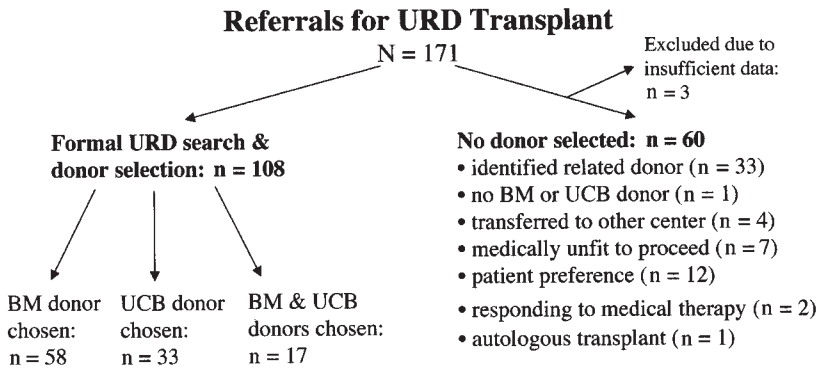

Figure 1. Summary of referrals for allogeneic transplantation and URD searches during the year 2000 at the University of Minnesota.

if there were no available related donors matched for 5 or 6 HLA-A,B,DRB1 antigens. Patients were eligible for unrelated UCBT if HLA-compatible unrelated BM donors were not available within 3 months of search initiation or if transplantation was considered urgent. HLA-compatible BM donors were defined as at least a 5/6 HLA-A,B,DRB1 match, unless the recipient was older than 35 years, in which case a 6/6 matched BM donor was required. UCB grafts were at least 4/6 HLA-A,B,DRB1 matched and had a cryopreserved cell dose of at least 1.5×10^7 nucleated cells (NC)/kg recipient body weight. Although the intent was to search for both types of HSC simultaneously for all patients, whether or not searches and donor selection were done for both types of HSC depended on patient size, diagnosis, urgency of transplantation, and available protocol. Urgent transplantations were defined as those needed as treatment for severe aplastic anemia, acute leukemia beyond first remission, advanced myelodysplasia, chronic myelogenous leukemia beyond chronic phase, or any malignancy that by history was unstable and unlikely to stay in remission for ≥3 months.

BM donors were identified through the National Marrow Donor Program (NMDP). UCB units were obtained from the Placental Blood Programs at the New York Blood Center, the St. Louis Cord Blood Bank, the Cord Blood Transplantation Study, and through Netcord. HLA typing was performed using the standard 2-stage complement-dependent microcytotoxicity assay, and antigens were assigned as defined by the World Health Organization HLA nomenclature committee. HLA-DRB1 type was determined by hybridization of polymerase chain reaction–amplified DNA with sequence-specific oligonucleotide probes with sequencing if needed. High-resolution Class II typing results for HLA-DRB1 were used to determine the selection of all URD grafts. Treatment protocols for URD BMT and UCBT were reviewed and approved by the Institutional Review Board of the University of Minnesota. Written informed consent was obtained from the patients prior to formal URD search and transplantation.

Data Collection

Data collected for all patients included age, weight, diagnosis, urgency of transplantation, and reason for selection of either BM or UCB. Search time was analyzed for all patients by obtaining the dates of preliminary search, formal search, and transplantation. For URD BM searches, the dates that the donor was identified and that the donor became available (ie, medically cleared and consent obtained) were documented, whereas for URD UCB searches, the date that the graft was chosen was recorded.

Statistical Analysis

The factors of age and weight were compared across graft sources by the general Wilcoxon test. Analysis of differences in the percentage of urgent cases was carried out using Pearson's chi-square test. For comparison, the time to obtain a URD graft was defined as "formal search to donor available." Dates for "donor identified" and "donor available" were identical for UCB grafts, whereas for BM searches "donor available" was the date of donor consent and medical clearance (see Figure 2). The general Wilcoxon test was used to compare search times between patients for whom only one type of search was performed. For the patients who had both URD BM and UCB searches, a paired *t* test was used to compare the difference in search times [6].

RESULTS

URD Referrals

Between January 1 and December 31, 2000, 171 pediatric and adult patients were referred for an allogeneic transplantation and URD search (Figure 1). Sixty patients did not proceed to a formal search and donor selection (reasons summarized in Figure 1). A total of 108 patients proceeded to a formal search and selection of a specific donor: either BM (ie, donor identified and cleared; n = 58) or UCB (ie, donor identified; n = 33) donors, or both (ie, BM donor identified and cleared and UCB also identified; n = 17).

UCB versus BM Searches

Further analysis of the search process for the 108 patients undergoing formal search and donor selection, with the reasons for the selection of either BM or UCB as stem cell source, is summarized in Table 1. Of the 32 patients (30%) that had both BM and UCB donors available to them but a BM donor was pursued, only 7 patients required urgent transplantation. Of the 24 patients (22%) for whom both BM and UCB donors were identified but a UCB donor was chosen, 16 required urgent transplantation. Twenty-one patients (19%) had a UCB donor chosen because no URD BM donor was identified. Overall, significantly more

Table 1. *Reasons for Selection of BM versus UCB as Stem Cell Source*

	No. (%)
Formal search and donor selection	**108**
URD BM donor selected only (ineligible for UCBT protocols)	**30 (28)**
BM and UCB available/BM chosen per doctor	**32 (30)**
BM and UCB available/UCB chosen per doctor	**24 (22)**
UCB as no URD BM donor	**21 (19)**
BM donor available but no UCB	**1 (1)**

patients who required urgent transplantation underwent UCB donor selection (54% of all UCB searches) compared to BM donor selection (21% of all BM searches) ($P < .01$).

Speed of Obtaining URD Grafts

For patients who underwent a URD BM search and donor selection (identification and clearance/consent), the median time from formal search to availability of a BM donor was 49 days (range, 32-293 days). The median time from formal search to availability of a donor for all UCB searches was 13.5 days (range, 2-387 days) (Figure 2). Analysis of the search times for patients undergoing exclusively BM or UCB donor selection revealed that a URD UCB graft can be obtained in a significantly shorter time than can a URD BM graft ($P < .01$) and that the additional time taken to obtain a BM donor was predominantly due to the additional 30-day interval (range, 10-101 days) required to clear the donor. For patients who had both a BM donor cleared and UCB chosen (n = 9), it took a mean of 29 more days (95% confidence interval, 21-37 days) to secure the BM donor than to secure the UCB donor ($P < .01$).

URD Transplantation

Characteristics of the 76 patients who proceeded to URD transplantation (BMT, n = 42; UCBT, n = 34) are summarized in Table 2. BMT recipients were older and heavier than UCBT recipients. The majority of BMT recipients received 6/6 HLA-matched grafts, whereas 97% of UCBT recipients received grafts with 1 to 2 HLA-antigen mismatches. The median infused cell dose for UCB recipients was 3.1×10^7 NC/kg (range, $1.2\text{-}19.0 \times 10^7$ NC/kg).

We next analyzed the speed at which patients could proceed to transplantation. Sixty-five percent of all UCBTs were considered urgent versus 14% of BMTs ($P < .01$). Although there were a greater number of urgent searches in the UCBT group, the UCB and BM groups did not differ in the time taken from the availability of the URD graft to transplantation (29 days in BMT versus 31 days in UCBT, P = NS). However, overall, patients proceeded to UCBT a median of 25 days sooner than did BMT patients ($P < .01$). Most of the additional time in the BMT group was due to the additional month required to obtain clearance for BM donation.

DISCUSSION

Availability of HLA-matched BM donors has been a problem, particularly for minority ethnic groups. For example, Caucasian patients are 30% more likely to find a potential 6/6 HLA-matched BM donor through the NMDP than are African American patients [2]. If extended matching of recipient-donor pairs via high-resolution analysis of Class I antigens proves valuable, this procedure may further limit the success in identifying a suitable BM donor. In the current report, we demonstrate that a significant number of patients referred to the University of Minnesota could be offered HSC transplantation because they had access to URD UCB when no appropriately matched URD BM donor was available. This greater access to URD UCB is possible because a greater degree of HLA disparity can be tolerated in UCBT without an increase in the incidence rates of GVHD and nonrelapse mortality, at least in pediatric recipients [4]. It is possible that if a population with an even higher representation of ethnic minority groups was similarly evaluated, the proportion of patients with potential UCB but no matched BM donors may be greater. Beatty et al. demonstrated that

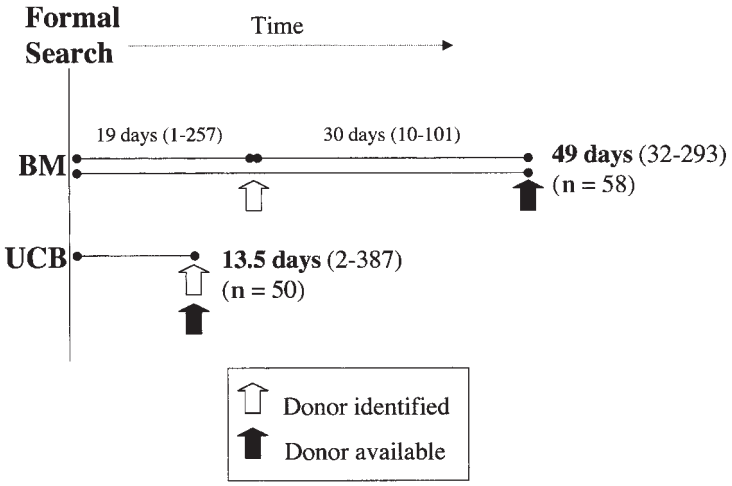

Figure 2. Comparison of time to identify and obtain a URD graft for 108 patients who underwent formal URD search and selection of a source of URD HSC. Cryopreserved UCB grafts are available on the day of identification. URD BM searches require the additional time to medically clear and obtain the consent of the donor (donor identified to donor available).

Table 2. *Comparison of Patient Characteristics for Transplant Recipients (n = 76)*

	BMT (n = 42)	UCBT (n = 34)	P
Age, median (range), y	28.4 (1.1-62.4)	11.5 (0.7-64.8)	.16
Weight, median (range), kg	67.0 (8-140)	45.8 (7.9-100)	.05
Diagnosis, n (%)			
Aplastic anemia	3 (7)	0	<.01
Hemoglobinopathy	0	1 (3)	
Immune deficiency	0	2 (6)	
Storage disease	11 (26)	3 (9)	
Heme malignancy	24 (57)	28 (82)	
Other	4 (10)	0	
Disease status, n (%)			
Advanced malignancy*	12/24 (50)	21/28 (71)	
Race, n (%)			
Caucasian	34 (81)	27 (79)	NS
African American	1 (2)	1 (3)	
Hispanic	1 (2)	2 (6)	
Native American	0	1 (3)	
Asian	1 (2)	1 (3)	
Unknown	5 (12)	2 (6)	
HLA disparity, n (%)			
Match	33 (79)	1 (3)	<.01
Mismatch	9 (21)	33 (97)	

*Defined as acute leukemias beyond the first complete remission or primary induction failures, chronic myelogenous leukemia post–blast crisis, or any hematological malignancy in relapse or unresponsive to chemotherapy.

for some ethnic groups, such as African Americans, genetic diversity is such that it will never be possible to create an URD BM bank able to supply all patients with 6/6 matched URD BM donors [7]. UCB offers a potential opportunity to provide access to HSC for such minority patients.

The major current barrier to wider use of UCBT is the problem of limited UCB cell dose. A proportion of patients in this study had both UCB and BM available, and in some instances of nonurgent transplantation, BM was selected because of concerns about graft cell dose. As experience with UCBT in adults increases, the lower limit of acceptable UCB cell dose may become better defined, and methods to augment graft dose are likely to be developed. Interestingly, we have noted an increase in the size of UCB units used for transplantation at our institution over the last 2 years (data not shown), likely because of the increased size of banks and improved collection techniques. We are currently investigating methods to overcome limited cell dose by infusion of 2 separate UCB units [8] or by ex vivo expansion.

This report details the experience of an institution that has a high level of expertise in searching for both BM and UCB grafts. This expertise is reflected in the greater speed with which our patients obtained BM grafts and proceeded to BMT, a median of 85 days compared to the median time of 4 months across the NMDP network [2]. Nonetheless, URD UCB has an advantage over BM in shortened search time, and most importantly, UCB patients were able to progress to transplantation approximately 1 month sooner than were those receiving BMT. This result is consistent with the findings of Rocha et al., who found in a retrospective study that the median time to transplantation was 4 weeks shorter for UCBT than for BMT [9]. The NMDP has recently introduced a new strategy to speed the search process for urgent URD BMT. This ultraurgent process can currently identify 5-6/6 matched BM donors in a median of 15 days from the start of the formal search (data provided by the NMDP, 2001). However, donors must still subsequently be cleared for donation, a process that accounts for the bulk of the additional time taken to obtain URD BM compared to UCB. Overall, UCB is likely to maintain its speed advantage. As the size and efficiency of UCB banks grow, UCB grafts may become obtainable even faster than occurs currently.

In this study, we confirm that use of URD UCB can extend the donor pool and that URD UCB grafts can be obtained more quickly than URD BM. The speed advantage of UCB may be of particular importance for those patients requiring urgent transplantation. In this series, the more rapid availability of UCB grafts resulted in a greater number of urgent cases receiving URD UCBT rather than BMT. This imbalance may be a potential bias when comparing outcomes of URD BMT and UCBT. The difference in time to obtain UCB and BM grafts will complicate a randomized comparison between UCBT and BMT. Ultimately, this difference in availability may confound a definitive comparison of the true merits of each HSC source.

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