ASBMT American Society for Blood and Marrow Transplantation

Optimizing Unrelated Donor Cord Blood Transplantation

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In contrast to the very high transplant-related mortality (TRM) associated with the early experience of cord blood (CB) transplantation (CBT), recent transplant series have been associated with comparable survival to that of human leucocyte antigen (HLA)-matched unrelated donor transplantation in children with similarly promising results in adults. Consequently, the use of CB as an alternative stem cell source and the global inventory of units in public banks are rapidly increasing although challenges remain. This review will address efforts to optimize CBT from 3 different perspectives: that of the transplant center, the CBT registry, and the CB bank.

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INTRODUCTION

Allogeneic hematopoietic stem cell (HSC) transplantation is limited by a lack of suitable donors. Cord blood (CB) has the advantage of ready availability and a reduced HLA match requirement [1-4]. Recent data suggests that CB therefore extends transplant access to racial and ethnic minorities (Table 1). In addition to the less than expected incidence of graft-versus-host disease (GVHD) [1-4], the GVHD after cord blood transplantation (CBT) may be easier to treat [5]. However, CBT can have major limitations primarily related to engraftment [1-4]. Therefore, to fulfill the promise of CBT it is important to consider all strategies by which CBT outcome can be optimized. This review will address this challenge from 3 vantage points: that of the transplant center (TC), the transplant registry, and the CB bank.

A TC PERSPECTIVE

When to Consider CB as a HSC Source

The first step to optimize CBT outcome is to consider CB as a potential alternative as soon as the patient is an allogeneic transplant candidate but does not have any suitable sibling donors and before the disease is far advanced. The TC must establish an unrelated donor (URD) HSC algorithm and decide how much HLA mismatch will be tolerated in HLA-A, B, C, DRB1, and DQ allele-typed URD before an alternate HSC source is sought. Prolonged URD searches can compromise the patient's care. Therefore, the TC should review the patient's HLA typing, the preliminary URD search, and the patient's ancestry, and assess the likelihood that a suitably matched URD will be secured in the required time period. For patients with less common HLA typing, especially non-Europeans, a simultaneous search for CB should be performed.

The CB Search

The CB search continues to be a challenge with no centralized search mechanism to access all units in the global inventory (Figure 1). Standardizing banking standards including the information needed by TCs should be a priority. In the meantime, to assist search coordinators the TC should establish: (1) what banks will be searched, (2) a unit selection algorithm that defines a satisfactory single unit, (3) criteria for a double-unit graft, and 4) whether backup units will be reserved in the event there are problems with shipping/thaw or graft failure. Factors to be considered in unit selection are summarized in Table 2.

The Preparative Regimen and Immune Suppression (IS)

Although the ideal conditioning for CBT is not defined, it is likely changes in conditioning and IS can improve CBT outcome. For example, consider the

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Table 1. Ancestry of 52 CBT Recipients at Memorial Sloan-Kettering Cancer Center 10/05-5/08

Patient Ancestry	N of CBT Recipients
Northwest Europe	4 (8%)
Eastern Europe	6 (12%)
Southern Europe	8 (15%)
European mix	8 (15%)
Asian	7 (13%)
African	10 (19%)
Hispanic/Latino	8 (15%)
Middle Eastern	1 (2%)
Total	52

improved survival reported with myeloablative double-unit CBT [6]. The single-unit historic controls were transplanted using cyclophosphamide (Cy) and total-body irradiation (TBI) with antithymocyte globulin (ATG) and cyclosporine-A (CSA)/methylprednisolone (MP) [4]. Although the double-unit transplants were also performed with Cy/TBI + CSA, the ATG and MP were substituted with fludarabine (Flu) and mycophenolate mofetil (MMF), possibly accounting for some of the improved outcome. This question is therefore being investigated in the Clinical Trials Network single- versus double-unit randomized trial in children utilizing Cy/Flu/TBI + CSA/MMF.

For patients who cannot tolerate high-dose conditioning reduced-intensity (RI) or nonmyeloablative (NMA) conditioning in patients with high-risk hematologic malignancies has been associated with an overall survival (OS) of 45% and progression-free survival (PFS) of 38% at 3 years [7]. A major question in NMA CBT is how to ensure engraftment in patients without recent exposure to combination chemotherapy or a prior autologous transplant (Figure 2) given the addition of ATG has been associated with a high incidence of posttransplant lymphoproliferative disease [8]. Investigation of preparative regimens that include agents that augment recipient IS without impacting the graft should be a priority in this patient population. Further, the efficacy of RI/NMA CBT in specific diseases should now be the subject of Phase II studies.

Although the ideal prophylaxis against GVHD in CBT has also not been established, CSA/MMF is relatively well tolerated in patients with intact renal function. Methotrexate should be avoided because of the risk of delayed engraftment. The use of ATG is associated with impaired immune recovery [8,9] and corticosteroids should likely similarly be avoided.

The CB Graft

Graft failure is a major risk associated with CBT, and from early in CBT experience it was recognized that the total nucleated cell (TNC) dose and the infused $CD34^+$ dose/kg were significant determinants of sustained donor engraftment. Perhaps the simplest strategy being investigated to augment engraftment is the infusion of a double-unit graft. This approach is as equally relevant to many children as adults, given graft failure remains a devastating feature of many pediatric series, and many larger children will only have access to units of relatively low cell dose.

Initial investigation with myeloablative double-unit CBT yielded a disease-free survival (DFS) of 57% [6] with updated analysis of 83 patients with

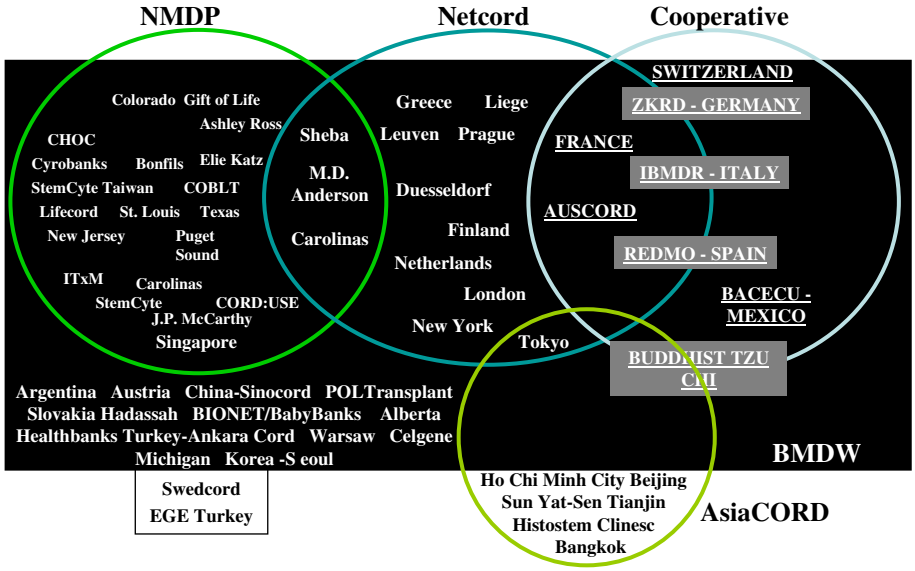

Figure 1. A schema representing the relationships between current CB banks. The banks contained within the intersecting circles will be searched by virtue of performing a search of the National Marrow Donor Program (NMDP), Netcord, and the NMDP Cooperative Registries ("Cooperative"), respectively. The black rectangle represents the banks that can be seen by performing a search of bone marrow donors worldwide (BMDW). Units in Swedcord and AsiaCORD were not listed in BMDW as of 4/08. The schema represents the complexity of CB searches. Creating a centralized search mechanism so that the global CB inventory can be easily accessed by transplant centers should be a priority. Reproduced with permission from Mary Halet, NMDP (updated as of April 2008).

Table 2. Major Criteria for Cord Blood Unit Selection

Criteria	Comments
HLA-A, B antigen, DRB1 allele match	Although HLA match requirement less stringent, HLA match still a critical determinant of TRM. Up to 2 mismatches acceptable, although how to trade off TNC dose and HLA match not known.
TNC dose/kg	Threshold for acceptable cell dose likely varies according to HLA match (the more mismatch the higher the required TNC). Use units < 2.5×10^7/kg with caution. Need to correct TNC of RBC replete units in order to compare to TNC of RBC depleted units.
Bank of origin	Quality of units can vary from unit to unit and bank to bank. Speed of turnaround time, reliability of unit information, and fees for unit testing can vary from bank to bank.
CT from attached segment	Only way to confirm unit identity.
IDMs and hemoglobinopathy testing	Should ensure completeness of testing so as not to slow down acquisition of the unit. Must be completed before unit is shipped.

HLA indicates human leucocyte antigen; TNC, total nucleated cell; RBC, red blood cell; CT, confirmatory HLA typing; IDMs, infectious disease markers.

high-risk hematologic malignancies showing a DFS of 54% (Professor John Wagner, personal communication). Engraftment appears improved after double-unit CBT despite only 1 relatively low cell dose unit engrafting, suggesting that the "losing" unit is facilitating the engraftment of the winner. Interestingly, analysis of postthaw $CD34^+$ cell viability has suggested that double-unit CBT is efficacious because it increases the chance of receiving at least 1 unit of high viability and thus with engraftment potential [10]. This suggests that postthaw $CD34^+$ cell viability could be an effective measure of unit quality and, unlike colony-forming unit (CFU) assays, is available on transplant day. Methods to determine unit quality both prior to and at thaw should be a major priority.

Although the poor engraftment and high TRM associated with low TNC dose in single-unit CBT has led to a focus on graft cell dose, unit selection is complicated by HLA match, also influencing engraftment and TRM. For example, in an analysis of 989 single-unit myeloablative CBT recipients facilitated by the New York Blood Center (NYBC), HLA-A, B antigen, DRB1 allele match was associated with significantly improved engraftment, less severe acute GVHD (aGVHD), lower TRM, and improved survival [11]. Therefore, the TC must decide how to choose between the smaller better matched versus the larger less matched unit. The NYBC analysis suggests that HLA match can partially compensate for lesser cell dose with a selection algorithm of 6 of 6 units, 5 of 6s $>2.5 \times 10^7$/kg, and 4/6s $>5.0 \times 10^7$/kg. However, many patients will not have access to such units, and some with such units will still not engraft. Clearly, more work is needed to resolve the dose versus match trade off.

The Thaw

The albumin-dextran dilution with centrifugation ("wash") thaw methodology is appropriate for small children but has been adopted for adult CBT as a matter of convention. However, a "no-wash" technique dilutes the product without centrifugation and is advantageous for adolescents and adults in whom even modest cell losses may be significant. This technique is faster, more efficient, reduces unit manipulation, speeds time to infusion, and reduces the potential for cell loss, and is still done in the controlled laboratory environment. This thaw has been adopted for patients over 20 kg at Memorial Sloan-Kettering Cancer Center (MSKCC) and in 50 double-unit CBT recipients has been associated with no serious infusion reactions and a high level of sustained donor engraftment (J. Barker, unpublished data).

GVHD, Infection, and Relapse

CBT has consistently demonstrated a lower than expected incidence of aGVHD and chronic GVHD (cGVHD) [1-4]. However, CB can be associated with severe GVHD, and transplant success is contingent upon therapeutic levels of a calcineurin inhibitor in the first months after transplant and how to transplant patients who cannot tolerate CSA is not established.

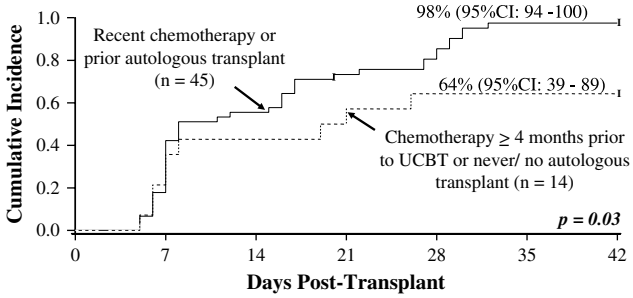

Figure 2. Association between prior chemotherapy exposure and sustained donor engraftment after non-myeloablative CBT. University of Minnesota data.

The nature of aGVHD after CBT and its response to therapy has yet to be examined in detail. However, Arora et al. [5] found more frequent therapy responses and a lower TRM in CBT recipients with cGVHD compared to predominantly HLA-matched URD BMT recipients. It is possible that some CBT recipients with GVHD may be successfully treated with less IS than is traditionally administered as therapy after adult donor transplants. This is another field requiring investigation in CBT.

Infection is a major challenge after CBT, and at many TCs infection-related mortality is the most frequent cause of CBT death, with the majority of deaths occurring within the first 3-4 months. Although aggressive supportive care to abrogate neutropenic sepsis and prevent fungal infections with extended spectrum azoles have led to decreased TRM, viral infections such as cytomegalovirus (CMV) or adenovirus remain a critical challenge in the early postengraftment period [12]. How to augment immune recovery is a major question. Cellular therapy approaches to the treatment of both infection and relapse, whereas challenging given the naïve neonatal immune system may yet show promise. In the interim, avoidance of ATG as well as aggressive supportive care including surveillance for viral reactivation is critical in early posttransplant. The single best strategy to prevent relapse is to refer the patient for transplant before disease is advanced or refractory. Measures to augment immune reconstitution assume greater importance given improved immune recovery has been associated with protection against leukemic relapse [13]. Interestingly, preliminary data has suggested that double-unit CBT may be associated with a reduced relapse risk [7,14].

A REGISTRY PERSPECTIVE

Since the first CBT from an HLA-identical sibling 20 years ago, progress in URD CBT has been paralleled by the development of CB banks worldwide. Today, at least 350,000 CB grafts are available in more than 45 banks and more than 14,000 CBT have been performed (V. Rocha, Eurocord, CIBMTR and Asian Pacific Registries). To evaluate CBT and foster research in CB biology the European Blood and Marrow Transplantation group (EBMT) established Eurocord in 1995. The Eurocord registry collaborates with the EBMT registry and Netcord banks collecting and validating clinical data from European and non-European patients transplanted with both Netcord and non-Netcord units. An important objective is to report to Netcord banks outcomes data concerning their units, a critical component of quality control. Other objectives are to monitor trends in CB use, analyze CBT outcomes, and assist clinicians in unit choice.

Changes in the Use of CB in Recent Years

From 1988 to March 2008, 4347 CBT have been reported to Eurocord from 415 European and non-European TCs including 44 countries with one-third from non-European centers. TCs have utilized related donors (n = 473, majority HLA-identical) for treatment of malignant and nonmalignant disorders with 3835 unrelated grafts. During the last 3 years unrelated CBT has increased to more than 500/year, and since 2004, adult CBT has overcome pediatric CBT (Eurocord registry data; Figure 3). Table 3 lists the URD CBT reported to Eurocord.

Risk Factor Analysis for Outcomes After Pediatric and Adult Cord Blood Transplantation

Retrospective registry studies have demonstrated the profound impact of cell dose (measured as TNC, CFUs, or $CD34^+$ cells) on engraftment, TRM, and survival [2-4,15]. More recently the prognostic importance of HLA disparity has became apparent [15]. Few series reporting outcomes after single-unit CBT for adults have been published with studies reporting DFS varying from 15%-76% [16-21]. Differences in outcomes can likely be explained by the heterogeneity in indications and disease status, CB graft selection, center effect, and the period of transplant. Eurocord

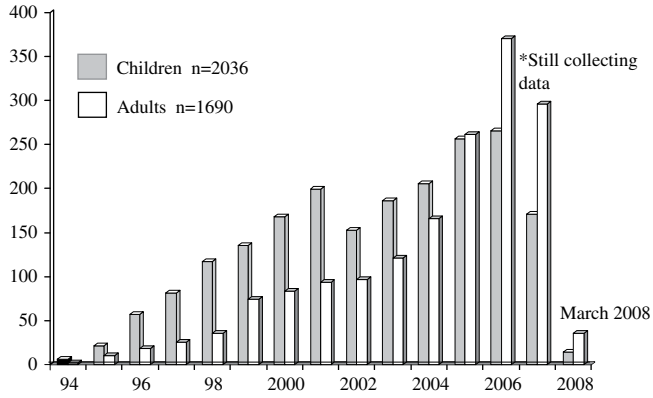

Figure 3. Unrelated CBT according to recipient age and year reported to Eurocord.

Table 3. Number of Unrelated CBTs Reported to the Eurocord Registry According to Recipient Age and Diagnosis

Diagnosis	Children ≤16 years (n = 2494)	Adults >16 years (n = 1727)
Acute lymphoblastic leukemia	38%	24%
Acute myeloid leukemia	16%	31%
Secondary acute leukemia	3%	6%
Myelodysplastic syndrome	5%	9%
Chronic myeloid leukemia	2%	11%
Chronic lymphocytic leukemia	—	1%
Hodgkin/Non-Hodgkin Lymphoma	2%	11%
Myeloma	—	2%
Solid tumors	—	0.5%
Histiocytosis	4%	—
Congenital and acquired BM Failure syndromes	10%	4%
Hemoglobinopathies	0.5%	—
Primary immunodeficiencies	11%	—
Metabolic diseases	8%	0.3%
Other diseases	0.5%	0.2%

BM = bone marrow.

has published the outcomes and risk factors after single unit myeloablative CBT in adults (n = 171) with hematologic malignancies since 1997 [20]. In summary: (1) a higher TNC dose >2.0 $\times$ 10^7/kg and use of hematopoietic growth factors were independently associated with faster neutrophil recovery; DFS and relapse were associated with advanced disease status. Two-year DFS for patients transplanted in early, intermediate, and advanced phases of disease were 41% ± 9%, 34% ± 10%, and 18% ± 4%, respectively. These findings mandate new approaches in adult CBT such as double-unit grafts and RI conditioning to circumvent the problem of low cell dose and high TRM.

Criteria for Cord Blood Unit Selection

Although infused TNC and $CD34^+$ dose are important risk factors for CBT outcome, the impact of HLA-match and other risk factors for OS and DFS have been controversial. Eurocord has analyzed 925 patients given a myeloablative single-unit CBT for malignant disorders from 1994 to 2005 [15]. The median age was 11 years with 37% adults, and the median follow-up of survivors was 28 months. Most patients (75%) had acute leukemia (20% early phase, 42% intermediate phase, and 38% advanced disease). The CB graft was HLA-matched (6 of 6) in 9%, 41% had 1 HLA mismatch, 41% 2 HLA mismatches, and 9% had 3 or 4. The median infused TNC dose was 3.1 $\times$ 10^7/kg, and the median infused $CD34^+$ dose was 1.4 $\times$ 10^5/kg (n = 667). The cumulative incidence (CI) of day 100 neutrophil recovery was 77%, and day 180 platelet recovery was 55%. The CI of day 100 grade II-IV aGVHD was 33%, with a day 100 TRM of 28%. At 3 years the CI of relapse and cGVHD were 23% and 29%, respectively. At 3 years estimated OS and DFS were 41% and 37%, respectively. In multivariate analysis increased early TRM was associated with increased HLA disparity (P = .0005), TNC dose <2 $\times$ 10^7/kg (P = .0002) and advanced disease (P = .01), whereas for relapse increasing number of HLA disparities (P = .0002) decreased relapse. In multivariate analysis for OS the most important factors were: (1) recipient CMV sero-status (P = .008), (2) early disease phase (P = .002), (3) infused TNC >2 $\times$ 10^7/kg (P = .008). However, only early disease status at CBT and infused TNC >2 $\times$ 10^7/kg (P = .02) were associated with better DFS in a multivariate model. Therefore, cell dose remains 1 of the most important risk factors associated with CBT outcome for patients with malignancy. Eurocord does not recommend single-unit CBT with a cryopreserved TNC dose <2.5 $\times$ 10^7/kg or <2 $\times$ 10^7/kg at infusion. The number of HLA disparities was not associated with OS or DFS because although it increased early TRM (Figure 4), in contrast to NYBC data [11], it decreased relapse in patients with malignancy. However, because of the risk of graft failure a CB graft should not contain more than 3 of 6 HLA disparities. A larger series of patients is needed to establish the acceptable TNC dose for each level of HLA mismatch, and further research is required to establish why the Eurocord and NYBC registries differ in their findings concerning the relationship between HLA disparity and relapse.

Outcomes Analysis of Reduced Intensity Conditioning (RIC) and Double-Unit Cord Blood Transplantation

Recently RIC regimens and double-unit grafts have extended the use of CBT in adults. In a Eurocord survey 74 adults (median 35 years) received myeloablative double-unit CBT for the treatment of acute leukemia. Median follow-up was 12 months, and median cryopreserved TNC dose was 3.5 $\times$ 10^7/kg. CI of day 60 neutrophil recovery was 80% and 1-year OS

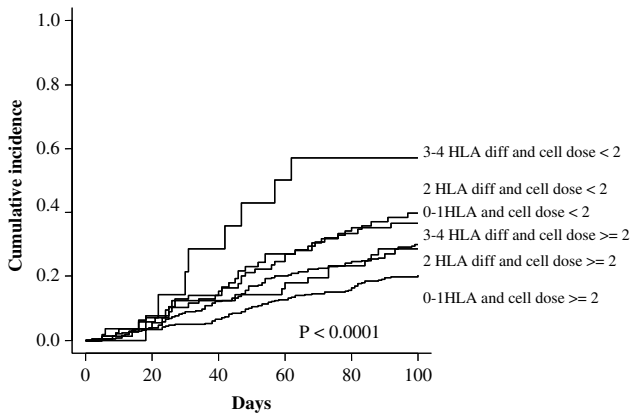

Figure 4. Transplant-related mortality in 925 CBT recipients with malignant diseases according to infused TNC Dose ($\times 10^7$/kg) and HLA disparity.

was 45% (V. Rocha, unpublished Eurocord data). These preliminary results show that double-unit CBT may be helpful to circumvent low cell dose but, longer follow-up of larger patient series is needed.

Recently, Eurocord, the French Society of Stem Cell Transplantation, and the University of Minnesota have analyzed outcomes after RI CBT using single units in 176 patients (median 45 years, 16-76) with hematologic malignancies: 116 acute leukemia, 36 lymphoid/plasma cell diseases, and 24 myelodysplasia (MDS)/myeloproliferative (MP) diseases (V. Rocha, unpublished Eurocord data). The median follow-up was 12 months (3-80) with 51% having advanced disease and 30% having prior autologous transplants. Conditioning varied according to disease and center. However, 95% received a Flu containing regimen including 55% Flu/Cy/TBI2Gy, 16% busulfan-containing regimen (<8 mg/kg), and 29% other combinations, with ATG in 23%. GVHD prophylaxis was most commonly (72%) CSA/MMF. All received a single unit graft that was 6 of 6 in 6%, 5 of 6 in 27%, 4 of 6 in 55%, and 3 of 6 in 11%. The median infused TNC was 2.7×10^7/kg. Day 60 neutrophil recovery was 78% ± 3%. In multivariate analysis, 3 factors were independently associated with neutrophil recovery: (1) TNC dose (< versus >2.7×10^7/kg, $P = .02$), (2) HLA-match (5-6 of 6 versus 3-4 of 6, $P = .04$), and (3) use of Flu/Cy/TBI versus other regimens ($P = .01$). Day 100 grade II-IV aGVHD was 30%. At 1 year 30% had cGVHD and TRM was 38%. Notably, 1-year TRM was 19% for patients given low-dose TBI (<6 Gy) and 61% without TBI, and 40% if low cell dose (<2.7×10^7/kg) compared to 21% for higher cell dose patients, and in multivariate analysis both low TNC dose and lack of TBI were associated with increased TRM. Relapse at 1 year was 41% and was associated with disease status at CBT. DFS was 41% for patients with acute leukemia, 31% if MDS/MP diseases, and 42% for lymphoid/plasma cell diseases. In a multivariate analysis advanced disease status ($P = .03$) and conditioning other than Flu/Cy/TB I2 Gy ($P = .004$) were associated with decreased DFS. Although TNC dose is a critical determinant of engraftment and TRM after RI CBT, the Flu/Cy/TBI2Gy provides better engraftment, reduced TRM, and better DFS. Despite short follow-up, these results support the use of this regimen as a strategy for broadening CBT to those previously excluded on the basis of age and comorbidities. Analysis of this regimen with double-unit grafts is underway.

THE BANK'S PERSPECTIVE

Standardization of CB Freezing and CFU Assays to Enhance the Quality of Banked CB Units

With the increasing numbers of CB collections worldwide and the variety of processing and freezing methodologies used by CB banks, evaluation of the quality of the graft has become an important focus. The National Cord Blood Program (NCBP) of the NYBC has used automated controlled rate freezing with the BioArchive® System since 1999. These freezers combine computer-controlled freezing with storage, thus eliminating the need to transfer the frozen CB unit to another freezer. Such a system limits the exposure of cryopreserved units to higher temperatures known as transient warming events (TWE). This is of great significance, given the NCBP has documented that TWE impair unit viability and CFU growth [22,23].

The Bioachive® System also strictly regulates the cooling and freezing rates for the 3 phases of the freezing process (prefreeze: from initial temperature to −3°C with a cooling rate of 10°C/min; freeze: from −3°C to −12°C; and a final phase with a slower temperature decline of 2°C/min to −50°C). Stringent monitoring of the cooling and freezing rates and the freezing curve for individual units and storage of the unit's freezing record allows for this information to be reviewed at any time as well as upon release of the CB unit for transplantation and analysis of the impact of this data on unit quality and transplant outcome. Analysis of the freezing profiles for over 40,000 banked units in a total of 16 BioArchive® freezers has revealed impressive similarity of the slope of the curves and very small numbers of "deviations," demonstrating that the CB freezing process can be standardized and is highly reproducible. The NCBP has introduced the review of the CB unit's freezing profile as a criterion for accepting the unit into the inventory, and investigation of the impact of the freezing profile of CB units from different freezers and different banks should be a priority for the CB field.

Precryopreservation testing of the cellular content of a CB unit includes the TNC, mononuclear cell, $CD34^+$ cell counts, and CFUs. The CFU assay is the only assay used in routine banking practice that determines the potency of the hematopoietic progenitors, and the NCBP has demonstrated that the CFU dose correlates with the speed of clinical engraftment [24]. However, the traditional CFU assay is limited by technical challenges, given that the evaluation of growth and enumeration of colonies is performed manually by light microscopy and is thus is time consuming, subjective, and very difficult to standardize among different laboratories. The NCBP have developed and implemented a computer-based system that automates colony staining with precise concentrations of 3-[4,5-dimethylthiazol-2yl]-2,5-diphenyltetrazolium bromide (MTT) and high-resolution digital imaging. This methodology allows testing of large numbers of samples in a "high throughput" assay. To date, more than 3000 CB units have been tested in duplicate (average: 30 CB samples/day) in the

NCBP CFU Laboratory. Importantly, 60 culture dishes can be processed in <2 hours, and digital imaging and storage permits a more precise analysis, classification, and enumeration of different colonies and assay standardization. Furthermore, colony images can be subsequently reviewed and prior to the release of a CB unit for transplantation. Utilization of this strategy for the evaluation of CFU growth from an attached segment of NCBP CB units is now underway. Results of the CFU assays as well as $CD34^+$ cell viability from thawed CB segments serve as a critical quality control measure for the entire cryopreservation process. Therefore, all NCBP units processed after August 2006 released for transplantation now have CFU assays performed prior to cryopreservation and prior to release from the attached segment. Analyses comparing these assays precryopreservation and postthaw, and correlation of the segment CFU assays and patient engraftment are underway.

Improving Transplant Access by a Highly Diverse Donor Inventory and Rapid Access to CB Grafts

Despite over 300,000 CB units stored worldwide [25], patients of ethnic minorities remain underserved. Equal access to transplantation for patients of all ethnic backgrounds has been an important goal of the National Cord Blood Inventory and diversity of donors is a hallmark of CB banking. The NCBP's current searchable inventory of approximately 45,000 units includes 9% Asian, 16% African-American, and 14% multirace donors. Notably, over 40% of the CB units released for transplantation are for patients of ethnic and racial minorities. Specifically, 19% of NCBP CBT recipients have been of African-American descent, and over 60% of those patients have received units from donors of the same race. Asian patients represent 5% of the total CBT recipients and of those over 50% have received units from Asian donors. The results of matching the donor and recipient race are more striking now than in the past, reflecting the increase in the inventory and access to large numbers of donors in the same ethnic groups.

One of the main advantages of CB grafts is their availability "upon demand." Therefore, the goal of the NCBP is to permit rapid access to units. All infectious disease and hemoglobinopathy testing as well as donor evaluations are completed before the CB unit becomes available for search. Thus, the only barrier to unit release is the final step of confirmation of unit identity by HLA typing of an attached segment. The NCBP HLA Laboratory is able to process requests for confirmatory HLA typing within 24-48 hours, in contrast to the 5-7 days routinely required by other laboratories. Therefore, the interval from search to actual transplant can be significantly shortened. Although the median time from the submission of a patient search to the shipment of a CB unit is 66 days (data for the period 10/2006-04/2008, n = 748 units shipped), a significant proportion of units are shipped within a few days: 123 units (16% during this period) were shipped in <30 days from search initiation. In real emergencies CB units have been released to TCs within 24 hours. Therefore, CB becomes the "graft of choice" in urgent situations.

Patients were offered CBT if allogeneic transplant was indicated and no suitably HLA matched related or URD were available in the required time period. Notably, 42% of patients were of non-North Western European ancestry with 50% of patients being non-European. In addition, the 4 patients of North-Western European ancestry had proven or potential 9-10 of 10 HLA-A, B, C, DRB1, or DQ allele matched URD but received CB because of transplant urgency (n = 1) or patient/MD preference (n = 3). CB grafts were 4-6 of 6 HLA-matched at A, B antigens and DRB1 alleles.

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