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REVIEW

Umbilical cord blood donation: public or private?

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Umbilical cord blood (UCB) is a graft source for patients with malignant or genetic diseases who can be cured by allogeneic hematopoietic cell transplantation (HCT), but who do not have an appropriately HLA-matched family or volunteer unrelated adult donor. Starting in the 1990s, unrelated UCB banks were established, accepting donations from term deliveries and storing UCB units for public use. An estimated 730 000 UCB units have been donated and stored to date and ~35 000 UCB transplants have been performed worldwide. Over the past 20 years, private and family banks have grown rapidly, storing ~4 million UCB units for a particular patient or family, usually charging an up-front and yearly storage fee; therefore, these banks are able to be financially sustainable without releasing UCB units. Private banks are not obligated to fulfill the same regulatory requirements of the public banks. The public banks have released ~30 times more UCB units for therapy. Some countries have transitioned to an integrated banking model, a hybrid of public and family banking. Today, pregnant women, their families, obstetrical providers and pediatricians are faced with multiple choices about the disposition of their newborn's cord blood. In this commentary, we review the progress of UCB banking technology; we also analyze the current data on pediatric and adult unrelated UCB, including the recent expansion of interest in transplantation for hemoglobinopathies, and discuss emerging studies on the use of autologous UCB for neurologic diseases and regenerative medicine. We will review worldwide approaches to UCB banking, ethical considerations, criteria for public and family banking, integrated banking ideas and future strategies for UCB banking.

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INTRODUCTION

Since the first umbilical cord blood transplantation (UCBT) in France in 1988, the growth of UCB banking to support the burgeoning interest in UCBT has been considerable. In 1991, Dr Pablo Rubinstein established the first unrelated UCB bank at the New York Blood Center supported by a pilot grant from the National Heart, Lung and Blood Institute.[1] Since that time, >160 public UCB banks have been established worldwide and there are ~730 000 UCB units available for public use.[2] Mothers may electively donate their infant's UCB to one of these public banks, and the UCB is banked and listed on a donor registry if the donor meets donor-screening criteria and the cord blood meets technical specifications. Not all donated UCB units are used for transplantation but if selected for patient use, there is no contact between donor and recipient. Private cord blood banks, which store UCB units for a particular family, usually for an up-front and yearly fee, are available worldwide. An estimated 4.0 million UCB units have been saved for private or family use. Hybrid banks, banking for families and for the public, have also emerged. Pregnant women in some locations may have the option for either public or private UCB banking or both. To aid in this decision, guidelines were established. In 2008, The American Society of Blood and Marrow Transplantation recommended donation to a public bank where possible, with the suggestion to review these recommendations in 5 years.[3] Both the American Academy of Pediatrics and the American Association of Obstetrics and Gynecology issued white papers recommending public donation unless there was a medical indication for autologous or related cord blood transplantation in the donor's family.[4,5] Although private banks marketed promises of future uses of autologous cord blood in regenerative medicine, the evidence for these claims was felt to be insufficient to support endorsement of private banking at the time. Recently, there is renewed interest in private banking, with emerging data on use of autologous UCBT in neurologic diseases and regenerative medicine. In addition, UCB licensure in the United States has increased the costs of public banking and unrelated donor UCBT. The options for donor sources for alternative donor hematopoietic cell transplant (HCT) have increased, with the increase in haploidentical HCT and mismatched unrelated donor HCT;[6] it is, therefore, appropriate and timely to review the data supporting private and public UCB banking options, current uses of UCBT for hematopoietic reconstitution as well as the potential use of UCB in the emerging fields of regenerative medicine and cellular therapies.

OVERVIEW OF BANKING TECHNOLOGY

The first UCB collection for transplantation occurred in Salisbury, NC. Dr Gordon Douglas from the New York University collected the UCB dripping from the umbilical cord into a sterile plastic bottle containing preservative-free heparin. The UCB was transported to Dr Hal Broxmeyer's laboratory where the unit was diluted with tissue culture media and DMSO, cryopreserved and stored under liquid nitrogen. Dr Broxmeyer transported the UCB in a dry shipper to Paris, France, where Dr Elaine Gluckman performed the first UCBT. The patient was a 5-year-old boy with marrow failure secondary to Fanconi anemia. The donor was his HLA-matched, non-affected, baby sister's UCB. He subsequently

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engrafted on day +19. He never developed any serious complications of transplantation and did not experience GvHD.[7] Now, 26 years later, the patient remains well and durably engrafted with his baby sister's UCB.

There have been enormous advances in the technical aspects of cord blood collection and banking since this first transplant. Initially, manual techniques for cord blood collection and processing for public banking were developed.[1] Collection into the anticoagulant citrate-phosphate-dextrose quickly became standard practice in public banks and has been adopted by most private banks. Although most banks depleted RBCs and plasma as a strategy for volume reduction during processing, a few isolated purer populations of mononuclear cells or utilized plasma reduction alone.[8] Cryopreservation using 10% DMSO or 10% DMSO in 50% dextran using controlled rate freezing was adopted. Methods for thawing and washing cord blood in dextran 40 and 5% human serum albumin and, later, dilution without washing were developed and implemented by many transplant centers.[1] Unfortunately, controlled trials to determine the optimal anticoagulant for collection, cryoprotectant for long-term storage or optimal thawing methods have never been conducted. UCB units that are not RBC depleted should be washed to remove cellular debris and to prevent serious infusion reactions.[9]

The Cord Blood Transplantation (COBLT) Study was the first prospective, open-label, study of UCB banking and transplantation in the world. Three additional public banks, at Duke, Children's Hospital of Orange County and University of California at Los Angeles, were established in the United States with this funding. Standard operating procedures for closed system cord blood collection, manual processing for RBC and plasma depletion and volume reduction were created, and tests for potency and viability were validated and published.[10]

As banked unrelated UCB was adopted as a source of cells for hematopoietic reconstitution, banking practices became more sophisticated. A series of devices for automated UCB processing were manufactured, including robotic cryopreservation systems. Currently, any validated method of processing is accepted. A network of cord blood banks in Europe, Asia, Australia and the United States, called Netcord, was established in 1997 and published the first standards for UCB banking. These were adopted by the Foundation for Accreditation of Cellular Therapies (FACT) and Joint Accreditation Committee of Europe (JACIE) and have been used for accreditation of UCB banks for over 15 years. In 2004, the American Association of Blood Banks (AABB) also published accreditation standards, and the Food and Drug Administration (FDA) issued guidance for UCB banking for unrelated transplantation in 2010. To date, five public banks in the United States have successfully completed the biologics licensure process with the FDA; there are no data to suggest that licensure has improved the quality of banked UCB units. A fee is charged of ~$25 000 to $40 000 to the transplant patient's insurance company when an UCB is selected for UCBT; for most banks, this is cost recovery, for the funds needed for collection, HLA typing, testing and storage, and because <10% of the UCB units in inventory have been used for UCBT. UCB units that are collected in public banks but do not meet criteria for storage (usually on the basis on nucleated cell count) are available for research use. In addition, UCB units stored in public banks can be used for a particular family if another child in the family develops a medical need for UCBT and the UCB unit is still available.

UCBT IN PEDIATRICS

After the first UCBT in a child with Fanconi anemia, selected transplant centers performed matched related UCBT in children with hematological malignancies or congenital marrow failure and showed that engraftment was feasible in children and the incidence of GvHD was low.[11,12] These encouraging results fueled the idea that UCB could be used in the unrelated donor setting without full HLA matching. In 1993, using a unit from the pilot unrelated donor bank established by Dr Pablo Rubinstein, the first UCBT was performed at Duke University in a 4-year-old boy with relapsed T-cell leukemia. The Duke group subsequently published the first report of a series of pediatric patients undergoing UCBT.[13] All reports confirmed that despite partial HLA mismatching, cord blood could engraft in smaller (< 40 kg) children, that cell dose was critical, that engraftment correlated with cell dose and that GvHD was reduced as compared with unrelated transplantation with adult donor cell sources.[14] Lower rates of engraftment were seen in diseases where resistance to engraftment was present such as acquired aplastic anemia, chronic myelogenous leukemia and hemoglobinopathies. These early results were later confirmed by reports from Eurocord and the Center for International Blood and Marrow Transplant Research (CIBMTR).[15–17]

UCBT was also applied to transplantation of children with inherited metabolic diseases where allogeneic bone marrow transplantation had been shown to be beneficial. UCBT was an ideal donor source for these young and small patients who rarely had a nonaffected related donor and needed to proceed to transplantation rapidly to prevent disease progression. Superior outcomes were demonstrated in Hurler syndrome, Krabbe disease, Metachromatic leukodystrophy and a series of rare inborn errors of metabolism.[18–22]

Related UCBT is curative in children with hemoglobinopathies.[23] The use of UCBT in these patients has been more challenging with a high incidence of graft failure and transplant-related mortality. Both related and unrelated UCBT have also benefitted children with congenital immunodeficiency and congenital marrow failure syndromes.

Today, the success of UCBT remains limited by a high incidence of transplant-related mortality and delayed immune reconstitution.[17,24] Various strategies to approach these challenges are under study. The Blood and Marrow Transplant Clinical Trials Network conducted a study to determine whether children with hematological malignancies would have improved survival after a double UCBT, as compared with single UCBT (BMT-CTN 0501). This study did not demonstrate an advantage for double UCBT in children where a single UCB provided an adequate cell dose.[24]

ADULT UCBT

Initial studies in single UCBT were hampered by delayed engraftment, leading to a high transplant-related mortality.[25] Outcome results have improved with better patient selection, better supportive care including growth factors, prophylactic and preemptive antiviral treatment and the choice of UCBT units with higher nucleated cell doses/kg (Figure 1).[26] More recent series in the United States, Europe and Japan have indicated disease-free survival of 40–70%, depending on patient age and disease status.[27–29] Reduced-intensity conditioning (RIC) has been employed to allow older patients and those with comorbid diseases to proceed safely to UCBT. Disease-free survival with the RIC approach has been reported at 40–60%.[30,31] Despite multiple retrospective analsyes, it it not clear whether single or double UCBT is superior in adults.[32]

IMPROVING ADULT UCBT OUTCOMES

Novel strategies to improve engraftment and survival in adult UCBT have included the use of *ex vivo* expansion, homing techniques and infection prevention regimens.[33] The Spanish groups pioneered the combination of a mismatched related or unrelated donor with a single UCBT; the haploidentical donor provides initial early engraftment and the UCB provides durable engraftment.[34] Elegant approaches to *ex vivo* expansion of cord

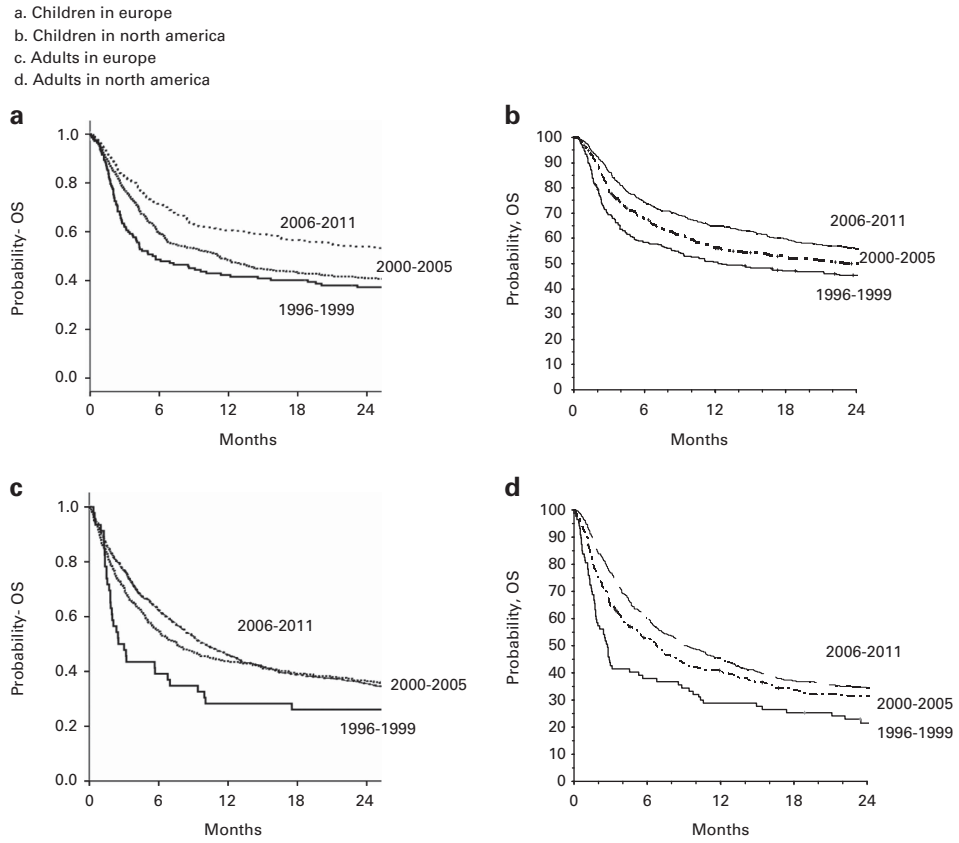

Figure 1. Overall survival (OS) at 2 years after UCBT for patients with AML, ALL and myelodysplastic syndrome (MDS) in Europe and North America (this figure was initially published in Ballen *et al.*,[26] reprinted with permission). (**a**) Children (≤16 years old) from Europe: UCBT period 1996–1999 ($N=142$), OS: $37\pm4\%$; 2000–2005 ($N=441$) OS: $41\pm2\%$; 2006–2011 ($N=749$) OS: $54\pm2\%$. (**b**) Children (≤16 years old) from North America: UCBT period 1996–1999 ($N=276$) OS: $45\pm6\%$; 2000–2005 ($N=843$) OS: $50\pm3\%$; 2006–2011 ($N=993$) OS: $56\pm6\%$. (**c**) Adults from Europe: UCBT period 1996–1999 ($N=46$), OS: 26 ± 6; 2000–2005 ($N=339$) OS: $37\pm3\%$; 2006–2011 ($N=1595$) OS: $36\pm2\%$. (**d**) Adults from North America: UCBT period 1996–1999 ($N=87$) OS: $22\pm8\%$; 2000–2005 ($N=359$) OS: $31\pm4\%$; 2006–2011 ($N=1210$) OS: $34\pm3\%$.

blood cells are under development by several academic and biotech groups. These include expansion on Notch Ligand, with nicotinamide, and on third-party mesenchymal stem cells.[35–37] Additional strategies to increase homing and migration of cord blood cells are also under development using prostaglandin E2, CD 26/dipeptidyl peptidase (DPP-IV) and Fucosylation.[38–40] All of these approaches are in early clinical trials and are showing promising results.[41] Strategies to support immune reconstitution are more challenging but the emergence of new antivirals (Chimerix CMX001) and third-party cytotoxic T lymphocytes appear to have benefit in pilot clinical trials.[42]

COMPARISON OF UCBT WITH OTHER ALTERNATIVE GRAFT SOURCES

Multiple retrospective studies have indicated comparable survival among single or double UCBT, matched unrelated donor, single allele mismatched unrelated donor and haploidentical donor transplants, with either myeloablative or RIC.[43] A study of 1593 lymphoma patients found similar overall among UCBT, 8/8 allele-matched unrelated bone marrow transplant and 7/8 allele-matched unrelated bone marrow transplant.[44] Chen *et al.*[45] described similar disease-free survival among patients treated with RIC receiving either double UCBT or matched unrelated donor PBSC transplants at a single center. Results with haploidentical transplant continue to improve with the use of post transplant cyclophosphamide, pioneered at Johns Hopkins.[46] The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) two parallel phase 2 trials showed comparable 1-year disease-free survival for patients with hematologic malignancy receiving either a haploidentical donor or double UCBT.[47] The BMT CTN is currently accruing patients to a randomized study of haploidentical vs double UCBT using the same RIC regimen. This information could impact the choice of public or private cord blood banking, as there are now more graft source options for patients.

PRIVATE UCB BANKING

Private UCB banking began in the United States in 1992. Parents are motivated to store UCB progenitor cells privately as a form of a medical insurance policy for the family of the baby, hence it is also known as family banking. The business model of family banks is that parents pay a fee to save their baby's UCB. The organization providing this service has a profit margin on each unit banked, and thus the provider is making money in real time and does not have to wait years to break even when units are released for therapy. Not surprisingly, this business model has enabled family banks to grow much faster than public banks.

Presently, in the United States, there is less government regulation of family than of public banks, but in many countries the operating standards applied by national health authorities are the same for family and public banks. Also, several family and public banks have business ties with each other, and some share the same laboratory, creating further confusion around whether to label a bank as family or public or hybrid or crossover and so on.

For the purposes of this review, we define a private or 'family cord blood bank' as an organization that markets UCB storage for family use and has its own laboratory for processing the UCB that it collects. Any other company that is only marketing family UCB storage but does not own a laboratory is called an 'affiliate.'

The Parent's Guide to Cord Blood Foundation began tracking family UCB banks in 1998. By the year 2001, there were 11 family banks in the United States (of which 8 are still in business) and 6 internationally: Canada (2), Germany, Hong Kong, Korea and Japan (all still operating). Today, there are ~215 family UCB banks located in 54 countries, plus at least 200 marketing affiliates serving over 70 countries. These totals are based on direct interviews with companies around the world. We have counted each laboratory that performs family storage as a 'bank', even though they may also conduct public banking. Specifically, some of the largest companies in family banking operate laboratories in multiple geographic regions, and each laboratory was counted despite their financial ties as one corporate entity. Counting banks at the laboratory level makes the most sense, because the quality of each UCB unit is based on the standards of the laboratory where it was processed and stored. Furthermore, in those companies that own multiple laboratories, the degree of accreditation by standards bodies such as AABB, FACT and ISO may vary from one laboratory to another.

As of 1 December 2014, an estimated 4.03 million cord blood units have been stored in family banks worldwide, including 1.26 million (31%) in the United States. The most recent World Marrow Donor Association inventory counted 731 000 cord blood units in public storage, including 260 000 (36%) in the United States. The Parent's Guide to Cord Blood Foundation performed a survey of family banks, asking for case reports of family UCB units released for therapies. From the survey respondents, there are 1015 case reports through the end of 2013, of which there are 530 autologous and 485 allogeneic transplants. Table 1 lists the 59 banks that participated in the survey.

The dominant category of autologous UCB use (82%) is 'brain injury,' that includes hypoxic ischemic encephalopathy, periventricular leukomalacia, cerebral palsy, ataxia, apraxia and traumatic brain injury, among others (Figure 2). The first use of autologous UCB from family storage as therapy for acquired neurologic injury was at Duke University Medical Center in 2005.[48] In this survey, the children treated at Duke had stored their UCB with 37 family banks in 21 countries.

Every year since 1998, a few family UCB units (~9% of the total autologous UCBT) are used to treat indications such as acquired aplastic anemia, neuroblastoma or medulloblastoma.[49] Very few of the cases have been published in the peer-reviewed literature. Of note, some autologous transplants were for leukemia, a treatment modality that almost never occurs in the United States because of the concern that there would be no GvL activity in an autologous graft and also because of the potential for contamination of UCB with malignant cells.[50]

Clinical trials for type 1 diabetes account for 7% of the autologous releases from family banks, but this treatment modality is currently not active because patient response to unmanipulated UCB stem cells was transient.[51] However, donor-derived β-cell engraftment has been demonstrated in recipients of UCBT, suggesting that pancreatic cell precursors are present in UCB units.[52] Further exploration of the use of cord blood in these patients will likely need to include immunomodulatory therapies in combination with UCB infusions.

Figure 3 illustrates the main categories of allogeneic therapy performed with family UCB units. We have not distinguished among the treatment centers in this chart because no one institution is dominant. Thirty-seven percent of the allogeneic therapies were UCBT to treat cancers of the blood, immune system and bone marrow. UCBT for hemoglobinopathies are the dominant (39%) allogeneic use of privately stored UCB, with 28% for thalassemia and 11% for sickle cell disease. The underlying trends with time and geography predict that in the future, UCBT for thalassemia from family banks in Asia will be the leading allogeneic use of privately stored UCB. Also, of note, except for one UK case, every sickle cell case in this report was banked and transplanted in the United States. Another 19% of allogeneic transplants were for 'other/rare' diagnoses. This includes genetic disorders such as Fanconi anemia, SCID, metabolic disorders, chronic granulomatous disease and so on. This survey accrued a disproportionate number of these diagnoses, relative to their epidemiology, because many family banks around the world operate 'directed donation' programs that offer free banking to

Table 1. Family banks participating in survey

Albert Einstein Hospital, Sao Paulo, Brazil
AlphaCord, USA
Banco de Cordon Umbilical (BCU), Mexico
Biocells Ecuador
Biohellenika, Greece
BIONET/BabyBanks, Taiwan
BioVault, UK
Cord Blood Registry, USA
Cell Care, Australia
Cells for Life, Canada
Cells4Life, UK
China Cord Blood Corp. (CCBC)—Guangdong & Beijing labs, China
Community Blood Services, USA
CorCell, USA (Cord Blood America Inc.)
Cord Blood Center, Romania
CordBank, New Zealand
Cordlife, Hong Kong
Cordlife, India
Cordlife, Singapore
CordVida, Brazil
Crioestaminal, Portugal
Cryobanks India, India
Cryo-Cell Mexico, Mexico
Cryo-Cell, USA
Cryolife, Hong Kong
Cryo-Save, Belgium
Eurocord-Slovakia, Slovak Republic
FamilyCord, USA
Gemabank (Human Stem Cells Inst.), Russia
General BioTechnology, USA
HealthBaby, Hong Kong
HealthBanks, Taiwan
ICTC, Peru
Insception Lifebank, Canada
LifebankUSA, USA
LifeCell, India
Matercell, Argentina
MAZE, USA
Medifreeze, Israel
New England Cord Blood Bank (NECBB),USA
Polish Stem Cells Bank (PBKM), Poland
Precious Cells, UK
Progenics Cord Blood Cryobank, Canada
Queensland Cord Blood Bank, Australia
Redcord, Colombia
Smart Cells, UK
Stem Care, Guatemala
Stem Cell Institute, Japan
StemCyte India, India
StemLife, Malaysia
StemOne Biologicals, India
Taburit, Israel
THAI StemLife, Thailand
ViaCord, USA
Virgin Health, UK
VITA34, Germany
Vivocell, Austria

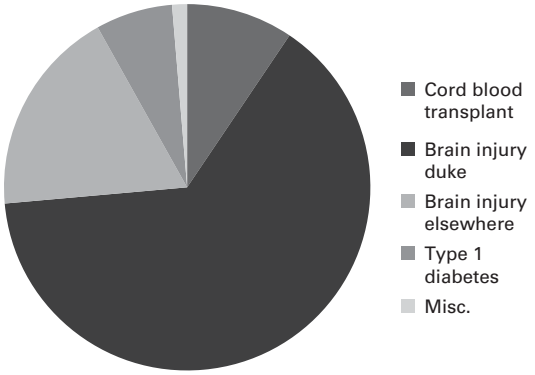

Figure 2. Autologous UCBT from family banks.

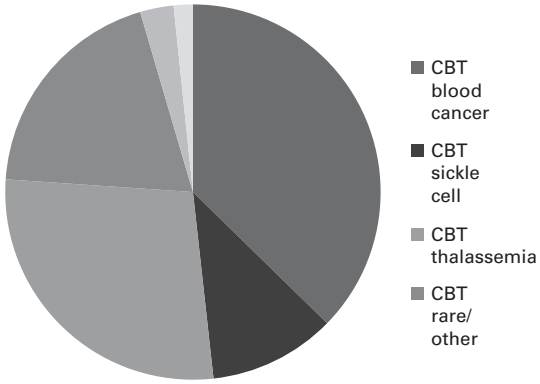

Figure 3. Allogeneic UCBT from family banks.

families in which an older child has a condition treatable by UCBT, such as sickle cell anemia or thalassemia.

In summary, through the end of 2013, the amount of cord blood inventory in private banks worldwide is ~6 times more than in public banks (at least 4 million versus 0.7 million), yet the public banks have released ~30 times more units for therapy (30 000 versus 1000). Table 2 explores the differences between private and public UCB banking. Privately stored UCB can be an important therapeutic resource for families in certain circumstances. One example is families where the donor child has a brain injury, and could use the UCB progenitor cells for autologous therapy. Another example is families where UCB from a baby sibling could provide a therapeutic transplant for an older child. The second pathway is particularly important in those nations of Asia and Africa where there is a high incidence of hemoglobinopathies.

CORD BLOOD THERAPY FOR ACQUIRED BRAIN INJURIES

Studies utilizing UCBT to treat children with inherited metabolic diseases demonstrated that donor cord blood cells could engraft in the central nervous system after myeloablative chemotherapy. In addition to expected enzyme replacement, improvements in cognition suggested additional beneficial effects of UCB cells. This led to the hypothesis that UCB infusions without chemotherapy could favorably alter the course of patients with acquired brain injuries. The Robertson Cell and Translational Therapy Program at Duke University initiated preclinical and clinical investigations in this area 5 years ago. Preclinical models at Duke and by others explored the potential benefit of UCB infusions in clinical models of hypoxic and demyelinating injuries.[53] Anti-inflammatory, proneurogenic and proangiogenic effects have been demonstrated. The safety of infusing cryopreserved autologous UCB cells intravenously in the outpatient setting was explored in 184 children with cerebral palsy and other similar brain injuries because of *in utero* stroke, hypoxic ischemic encephalopathy, intraventricular hemorrhage, prematurity, near drowning and other hypoxic insults and showed that the approach was safe and well tolerated. The varying quality of UCB units obtained from a number of private banks was also demonstrated, highlighting the need for increased regulations and standardization of UCB unit collection, processing, testing and storage procedures for privately banked units to be used in the clinic.[48]

A phase I trial of fresh, volume-reduced, RBC-reduced autologous UCB infusions in babies with hypoxic ischemic encephalopathy also treated with cooling showed that this approach was safe and beneficial as compared with a concomitant cooled-only control.[54] A phase II randomized trial is planned and will be needed to confirm these efficacy results. A phase II/III randomized, placebo-controlled, crossover clinical trial testing the efficacy of cryopreserved autologous UCB infusions in children with cerebral palsy has competed accrual at Duke and will be analyzed in the second quarter of 2015. A safety trial of autologous UCB infusions in children with autism is also underway. If these studies show benefit, they will alter the paradigm of private and public UCB banking for the future. Private banks that wish to release UCB units as therapy for brain injury will be required to meet standards for donor eligibility and screening, pre-cryopreservation testing and stability, similar to public banks. For public banks, studies for safe and effective utilization of allogeneic UCB cells without myeloablative chemotherapy will need to be conducted to understand whether allogeneic cells will exert paracrine effects and whether partial HLA matching or short-term immunosuppression will be needed to optimize efficacy of these cells.

REGENERATIVE MEDICINE

UCB cells, compared with adult bone marrow, are less mature, have longer telomeres and greater proliferative potential. Reports of engraftment of lineage-specific, nonhematopoietic cells in recipients of UCBT raise the possibility that UCB contains rare embryonic-like cells or early, committed progenitor cells of nonhematopoietic lineages.[55] Additional properties of UCB cells include paracrine signaling, producing anti-inflammatory as well as pro-angiogenic and pro-neurogenic effects. Adaptation of UCBT to minimize the need for pretransplant chemotherapy will be necessary to reduce traditional transplantation risks. With modifications, UCB infusions have significant potential for the treatment of cardiac, neurologic and vascular diseases (Table 3). Cerebral vascular accident is the third leading cause of death among adults, and a major cause of morbidity and health-care costs. Reducing the extension of stroke is a major goal of regenerative medicine studies. UCB cells have produced functional recovery and vascular remodeling after stroke.[56] UCB has shown promise and is in clinical trials for the treatment of patients with chronic spinal cord injury.[57] The IV infusions of human UCB ameliorated the consequences of prenatal hypoxic injury in a baby rabbit model of hypoxic ischemic encephalopathy.[58] Mesenchymal stromal cells, isolated from placenta or cord tissue, show promise for treatment of patients with brain injuries, degenerative brain diseases, peripheral vascular disease and spinal cord injury.[59]

If UCBT proves successful as regenerative medicine therapy for common degenerative diseases, the numbers of UCBT may rise steeply; in addition, there may be momentum to bank UCB privately, so as to be available for personal use. As it is highly unlikely that every patient needing this type of therapy could have their own UCB stored, safe methods to use the hundreds of thousands of publically banked, fully qualified and HLA-typed, allogeneic UCB units in regenerative medicine should be developed.

Table 2. Advantages and disadvantages of private and public cord blood banking

Consideration	*Private*	*Public*
Banking motivation	Health insurance for the baby and first-degree relatives	Be the match to save a patient in need
Cost to parent	First year $1300–$2300, over 20 years, ~$4000 (USA)	Free
Business model of bank	Profit margin on each cord blood unit banked	Must sell cord blood units for transplants to break even
US FDA requirements	Registered Inspected	Registered Inspected Biologics license
Directed donations accepted?	Yes	Yes
Inventory available to unrelated patients	No	Yes
Inventory suitable for unrelated patients	No	Yes
Odds of cord blood storage	All samples big enough for regenerative therapy are kept	Over 80–90% collections are discarded
Cord blood Transplants to date	~1000	~35 000
Collection area	National	Selected hospitals that are often local to the bank
Additional stem cell storage options	May store additional stem cells from cord tissue and/or placenta	None
Therapy partnerships	Bank may offer exclusive access to clinical trials they sponsor	Usually nonexclusive

Abbreviation: FDA = Food and Drug Administration.

Table 3. Regenerative medicine approaches for the use of cord blood

Approach	*Disease*	*Investigator*	N	*Results*	*Current trial*
Fresh autologous UCB	Hypoxic brain injury at birth	Cotten *et al.*[54]	23	Improved function at 1 year	NCT01072370
Autologous UCB	Cerebral palsy	Sun *et al.*[48]	184	Parental reports of improved function	NCT01072370
BM-MSC	Acute MI	Jeevanantahm *et al.*[69]	Meta analysis	Improved LV function	NCT01569178
Intramuscular UCB	Limb ischemia	Perotti *et al.*[70]	Case report	Healing ulcers	NCT01019681
Autologous UCB	Type I diabetes	Haller *et al.*[51]	24	Increased insulin requirements	
Allogeneic UCB or bone marrow	Epidermolysis bullosa	Wagner *et al.*[71]	6	Partial correction of collagen deficiency	

Abbreviations: BM = bone marrow; LV = left ventricular; MI = myocardial infarction; MSC = mesenchymal stem cell; UCB = umbilical cord blood.

ETHICAL CONSIDERATIONS

Ethical issues regarding public and private UCB storage, marketing practices and recruitment have been reviewed in detail.[60] Education of mothers, obstetrical providers and pediatricians on the current uses of UCB is essential. If the studies on autologous UCBT for cerebral palsy show a benefit, expectant mothers at risk of premature birth should be informed about private banking as UCB are not collected from premature babies for public use, premature babies are at higher risk of cerebral palsy and UCB from premature babies have higher CD34+ cell counts.[61] Discussion of the potential for UCB in regenerative medicine should be presented as speculation until further evidence of benefit is determined. Access to family banking for families with a medical indication (for example, sibling with leukemia, sickle cell anemia, thalassemia, congenital marrow failure or immunodeficiency (inherited metabolic diseases)) should be available to all qualifying families regardless of finances. Crossover banking, a private/public bank option in which UCB units can be used for either public or private use, has been proposed as a solution to promote both autologous and unrelated UCBT. The regulations surrounding UCB banks are different for public and family banks, especially in the United States, and differences in quality (higher rate of bacterial contamination, lower viable CD34+ cell dose in family banks) have been documented.[48] Hybrid banks have been established in Europe, Asia, and Middle East.[62] In Italy, a study of 1309 UCB units collected for autologous UCB banking allowed units to be separated by total nucleated cell count, with larger units potentially being eligible for unrelated use and smaller units for family-directed use.[63] The authors conclude that the integrated bank model would increase public UCBT with a reduction in national health-care system costs as private money is being used to expand public inventory, and the quality of autologous UCB would be improved. Family banking is not available to all as a fee is charged, between US $1350 to $2300 initially at accredited banks and a yearly storage fee of $100 to $175.[64]

In Spain, for example, public banks will store UCB for autologous use, but only if it is also available if requested on behalf of an unrelated patient.[65] A survey of potential Swiss donors revealed that 49% would accept a hybrid private/public model.[66] In Australia, recruitment to clinical trials of autologous UCBT has been influenced by differences in policy between public and family banks.[67] Family UCB banks may also serve as a source

of related UCB donors, particularly for patients with hemoglobinopathies who reside in countries without access to large public banks.[68]

CONCLUSIONS

The field of UCB banking and transplantation has grown dramatically in the past 25 years as technology for both autologous and unrelated UCBT has improved. Pregnant women today have a variety of options, including public or private UCB banking. UCB is one of several sources of allogeneic hematopoietic stem cells available for transplantation. A randomized study comparing UCBT and haploidentical HCT in adults is in progress. On the autologous side, encouraging studies in neurologic disorders are underway for patients with cerebral palsy, stroke and other common diseases. We are at an exciting juncture in the field as both private and public banks may serve an important purpose. Crossover banks, where donations can be moved to public use if not needed by a particular family, might be a future option, but would necessitate private banks operating at the same standards as public banks. Although we continue to recommend donation to a public bank where feasible, private storage may indeed serve a purpose when medically indicated and as 'medical insurance' if regenerative techniques prove fruitful.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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