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STEM CELL BIOLOGY

Umbilical cord blood banking: an update

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Abstract
Background Umbilical cord blood is a potential vast source of primitive hematopoietic stem and progenitor cells available for clinical application to reconstitute the hematopoietic system and/or restore immunological function in affected individuals requiring treatment. Cord blood can be used as an alternative source for bone marrow transplantation and its use is developing into a new field of treatment for pediatric and adult patients presenting with hematological disorders, immunological defects and specific genetic diseases.
Discussion More than 25,000 allogeneic cord blood transplantations have been performed worldwide since the first cord blood transplantation in 1988. There are two banking options for storing umbilical cord blood [private (family) and public]. Cord blood stored in private banks are used for either autologous or allogeneic transplants for the infant donor or related family members but private cord blood banks are not searchable or available to the public. More than 780,000 cord blood units are stored in over 130 private cord blood banks, worldwide, and over 400,000 units in more than 100 quality controlled public cord blood banks.
Conclusions Researchers continue to evaluate the usefulness of cord blood cells in treating human diseases or disorders for purposes other than hematological disorders including heart disease, strokes, brain or spinal cord injuries and cancer. This review summarizes the status of umbilical cord blood banking, its history and current and potential use in the treatment of human disease.

Keywords Umbilical cord blood · Public and private cord blood banks · Transplantation · Clinical applications · Regenerative medicine

Capsule Umbilical cord blood which is readily available and stored in either private or public cord blood banks is an alternative source of cells for transplantation purposes for pediatric and adult patients with malignancies, hemoglobinopathies, metabolic disorders, immune deficiences and potentially for regenerative applications.

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Introduction

Umbilical cord blood can be used as a source of primitive hematopoietic stem and pluripotent progenitor cells in clinical application to reconstitute the hematopoietic system and/or to restore immunological function in vivo. It has been used successfully as an alternative to bone marrow or peripheral blood progenitor cells for transplantation purposes and developing into a new field of study in medicine for treating diseases. Cord blood is considered a treatment option in pediatric and adult patients with hematologic malignancies and disorders (leukemia, thalassemia, sickle cell disease, etc.), bone marrow failures, inherited metabolic disorders, immunological defects and other genetic diseases [1–12]. Double umbilical cord blood grafts, that use cord blood units from two donors, mitigate cell dose limitations for larger children and adults with malignant disorders [12–14]. There is a continual need for suitable donors for one third of all patients in need of bone marrow transplants in which no available human leukocyte antigen (HLA) matched donors are found [15]. Thus, umbilical cord blood as single or double unit transplants, provide a potentially vast source of hematopoietic stem cells, and represent a valuable alternative for stem cell transplantation needs worldwide and with the

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added potential of decreased chronic graft versus host disease (GvHD) compared with bone marrow and peripheral blood progenitor cell donors [13, 16, 17].

More than 25,000 allogeneic cord blood transplantations have been performed worldwide since the first cord blood transplantation in 1988 in a patient from Paris, France with Fanconi anemia using an identical HLA matched sibling [8, 18]. The results, to date, are encouraging and appear at least comparable to bone marrow or peripheral blood progenitor cells as the donor source for transplants [12, 13]. Later, Rubenstein and others were the first to establish an unrelated cord blood bank from voluntary donors and then used the blood units from the bank for unrelated cord blood transplantation [19–21]. These events further emphasize the importance of umbilical cord blood banking for transplantation in the medical field and the growing interest with 330 published articles retrieved by online searching of the PubMED website (www.ncbi.nlm.nih.gov/pubmed) on January 11, 2011 using the term "umbilical cord blood banking".

Over 400,000 cord blood units are now stored for use in more than 100 quality controlled public international cord blood banks [8, 22, 23]. Stored cord blood samples have been used for transplants in both children and adults having malignant or non-malignant diseases [1–8, 10–14, 22]. To further expand and develop this service, national and international networks, following agreed upon standards and protocols for collection, processing and handling of stored blood, have culminated in establishing registries and for accreditation practices. In 1998, the foundation NETCORD (http://www.netcord.org) was developed to establish an international registry for cord blood banks and procedures with standards for the safe exchange and clinical use of banked cord blood. Approximately one-half of United States cord blood banks have been certified following standards and accreditation procedures by the AABB (formerly American Association of Blood Banks) [22]. Furthermore, the NetCord-Foundation for the Accreditation of Cellular Therapy (FACT) was established and led to international standards for accreditation in 2000 of cord blood collection, processing, testing, banking, selection and later published in 2008 [24]. There are now two international registries: NETCORD, which lists cord blood units only and Bone Marrow Donors Worldwide which lists both bone marrow and cord blood donors [22]. EuroCord and the Center for International Blood and Marrow Transplant Research (CIBMTR) provide extensive analytical expertise in evaluating efficacy and outcomes [4, 10, 12].

Cord blood banking options: private and public

Two cord blood banking options are available: private (or family) and public. Approved public cord blood banks are available for all donors and receives umbilical cord blood following informed parental consent. The cord blood units will then belong to the public bank for later use. The inventory is registered and later searched by the public and healthcare providers to access information for transplantation sources. Prior to inclusion in the registry, samples are screened based on volume, cell number and tissue types, health history and infectious disease status. Conversely, private cord blood banks obtain blood samples and store the cord blood for individual use by families and become the property of the child under the guardianship of the parents. The samples are more costly to collect and maintain in private banks. Cord blood samples stored in private banks for either autologous or allogeneic transplants for the infant donor or related family members are not searchable or available to the public [17, 22, 25]. Currently, 134 private cord blood banks worldwide are known to store more than 780,000 units [26].

A major criticism of private banks is that the infant for whom the blood is banked will likely never need the stored blood and the blood is not accessible by the general public for use. This point is illustrated by Ballen and colleagues [26] with an estimated 0.04% to 0.005% chance that an individual will develop a disease treatable with their own stored cord blood by 21 years of age using a hematopoietic transplant approach. Johnson [27] reported that a smaller proportion of individuals (e.g., 1/2,700 and 1/1,400) would be candidates for using autologous or allogeneic transplants in their siblings, respectively. These probability estimates would equate to the incidence of cystic fibrosis (1/3,000), spina bifida (1/800) and Down syndrome (1/700) in the general population in which testing is routinely discussed with the parents during the pregnancy. Therefore, researchers continue to evaluate the usefulness of cord blood cells for other purposes than hematological disorders such as repairing damage caused by heart disease and infarcts, diabetes mellitus, strokes, traumatic brain or spinal cord injuries in addition to malignancy [8, 17, 22, 25].

It is noteworthy, that the origin of certain acute leukemias has been tracked to pre-leukemic cells found in newborns from stored neonatal blood spot cards [28]. Cells from other cancers, as well, may reside in the donor source for autologous grafts, therefore, transplants using autologous cord blood for treating the donor in the future may be less likely used to treat hematologic malignancies. These potential concerns for future use of cord blood in transplantation should be addressed when cord blood banking is first discussed with the parents and, thus, before the donor requires a transplant (e.g., if leukemia develops). However, the presence of pre-leukemia cells would be an issue for both private and public cord blood banking and their intended uses in the future, but should not be solely a contraindication for cord blood collection and storage. Healthcare providers should, therefore, inform the interest-

ed birthing parents about the advantages and possible disadvantages of cord blood banking and related future cord blood usage. They should be prepared to discuss scientific, legal and ethical issues when the parents and families are provided cord blood banking information during pregnancy [8, 17, 22].

During the past 15 years, cord blood banking has become more accessible for families due to better public awareness and a greater potential to treat diseases, but yet a vast majority of Americans when offered have not used cord blood banking services [17]. For the vast majority of families, due to cost or other reasons, public cord blood banking represents the only option to obtain a suitable graft in case of a need. Thus, it is important to educate prospective parents on the advantages and disadvantages of private versus public cord blood banking before the third trimester of pregnancy [21]. The donor process should be clear and simple with ample time to ask questions and to have the opportunity to become informed regarding the issues related to cord blood banking for their family. Presently, about 20% of US states have enacted legislation to ensure that families are educated regarding their options with respect to both public and private cord blood banking.

Significant advances demonstrated by early results suggest that the use of cord blood and stem cells in humans with public awareness will continue to expand with the inclusion of more diseases, treatment options and the emerging field of regenerative medicine. Information needs to be shared on potential uses and contraindications (and costs - about $1,500 for storage and collection for private blood banking) of cord blood banking and the pros/cons of public and private banks [29]. For example, the American Academy of Pediatrics (AAP) and American Society for Blood and Marrow Transplantation (ASBMT) support the use of private cord blood storage when a full sibling has a medical condition (malignant or genetic) and could benefit from cord blood transplantation [26, 30]. Otherwise, they recommend public banking with the understanding that cord blood stored in a public bank may not be available for private use when needed by the donor or a family member. In addition, several minority groups (e.g., African–Americans, Hispanics and American Indian/Alaskan Native) are also under represented in cord blood bank registries.

Recent evidence indicates that cell count and volume are key parameters for eligibility of cord blood units for storage. Approximately one-fourth of all collected cord blood units meets the established criteria for storage. Unlike public banks utilizing established criteria for storage in cord banks, private banks generally store all collected cord blood units. Sun et al. [31] reported that quality parameter of privately banked cord blood units are inferior to public banks. The main reasons for exclusion include insufficient volume, delayed arrival of specimen at processing sites and a low cell count. The ethnic background of the donor also plays a role in this process and for data collection [8]. The under representation of minorities in registries should be addressed in the future by educating the public and better recruitment practices to increase blood donor sources for transplantation purposes.

Cord blood banking protocols and standards

The donor selection process for umbilical cord blood banks is carefully conducted and generally a family history is collected to minimize the potential risk of transmitting unrecognized hereditary disorders that could impact on the recipient. Cord blood may not be collected if there are known hereditary diseases specifically involving hematopoiesis in the family or if severe disabilities or diseases are identified in the donor fetus before birth. Additional exclusion criteria include infectious diseases (e.g., HIV, hepatitis) in the mother, severe pregnancy complications or premature delivery with birth weight less than 1,500 g or if perinatal asphyxia is present in the fetus and cell counts [8, 21, 32]. These factors would impact on the quality and quantity of cord blood collected. The mother must consent before thorough testing for infectious diseases, recording of medical or clinical information to be added to the dataset and for HLA typing to be completed before the collection and storage of cord blood in the public bank for future transplantation purposes. The collection of cord blood, in general, must not affect the delivery of the baby and should only be performed by trained staff (e.g., physicians and midwives) who are knowledgeable about cord blood collection, processing and handling for screening, transportation and storage. To address issues related to cord blood banking, the Eurocord registry was established in 1999 in Europe with the responsibility for collecting and analyzing clinical outcomes on cord blood transplantation. The American registry CIBMTR reports information regarding cord blood banking and transplantation clinical outcomes [9, 10, 12].

The recommended protocol for umbilical cord blood collection, after the birth of the infant and before the placenta is delivered, is to clamp the umbilical cord and thoroughly clean and disinfect to prevent contamination with maternal blood or by infectious agents. The umbilical cord is then punctured under sterile conditions to allow the blood to flow freely and be assisted by gravity into an anticoagulated sterile collection bag. The storage and transport temperature should be maintained at 22°±4°C. The cord blood is then labeled, weighed and the volume recorded. The blood cell counts for nucleated, mononucleated and CD34+ cells are recorded before the blood units are stored in liquid nitrogen or in the vapor phase of liquid nitrogen

(≤150°C) [8, 21]. The cell count and volume are known to be key parameters for selection and eligibility of cord blood units for transplantation. Cord blood can effectively be frozen in glycerol, but 10% or less dimethyl sulfoxide is more commonly used today as the cryopreservative of choice and can last in liquid for decades if not for a lifetime without significant degradation or loss of potency [33]. For example, the German Red Cross, Mannheim Cord Blood Bank samples have been stored for more than one decade and used successfully elsewhere for transplant purposes [8]. Washing thawed cord blood to remove DMSO prior to infusion may not be necessary [34].

The total number of nucleated cells that are transplanted strongly correlates with the clinical outcome. A minimum of 2.5×10^7 total nucleated cells per kilogram of recipient's weight is generally required. The average cord blood unit contains about 1×10^9 total nucleated cells [10, 25]. The use of two cord blood units is often requested to transplant adults which appear to lead to a better outcome [35]. A greater incidence of acute GvHD occurs following double unit cord blood transplantation. Ex vivo expanded T regulatory cells may decrease occurrence of this adverse event [13, 36]. The main obstacle in the use of cord blood transplants in adults has been the risk for graft failure and delayed hematopoietic recovery. This is primarily due to the larger size of an adult requiring more blood compared to an infant or child being transplanted and the number of hematopoietic stem cells required for a successful transplant outcome [22].

However, even among siblings, cord blood samples should be HLA matched, if possible, before transplantation. For siblings, there is a 25% chance of a six for six haplo-identical HLA match, which is ideal for transplantation, and a 75% chance of at least a three for six haplo-identical HLA match. The three for six HLA match is considered at the threshold for an acceptable transplant [9–11, 36]. Families are also more likely to find an equivalent or preferable HLA match within extended family members than in a public bank of unrelated donors. However, success in finding donors depends on the size of the family and the size and diversity of the public cord bank. At present, there are more than one million cord blood units stored in private banks available for autologous transplants or for other future application [37]. Yet, a relatively small number of cord blood units have been used and with unknown or unreported clinical outcomes and long-term follow up studies. Hence, many ethical issues are raised [37] when deciding about cord blood banks. Families should consider the once in a lifetime opportunity to collect and save cord blood and become aware of future gene therapy, immune modulation or for restorative or regenerative treatment, an emerging area of investigation in this growing field of study.

Cord blood banking experience to date

Reporting of experiences and data collected from established international public cord blood banks are required to gain a better understanding of the status and use of cord blood banking and clinical outcomes [23]. We summarized selected reports from the literature and divided into two sections, *Hematology Disorders/Oncology* and *Non-Oncology*, on the use of cord blood by individual investigators and centers as well as pooled data from several sites.

Hematology disorders/oncology

The Cord Blood Transplantation Study (COBLT) first reported in 2008 on the outcomes in 191 children (mean age 7.7 years) with hematologic malignances [11]. The median time to neutrophil engraftment was 27 days and 174 days for platelets. Acute GvHD III/IV by day 100 was 19.5% and that for chronic GvHD was 20.8%. However, high resolution HLA matching did decrease the occurrence of severe acute GvHD.

Cohen et al. [10] later pooled data from CIBMTR, the New York Blood Center National Cord Blood Program, and Eurocord-Netcord that included 514 patients receiving unrelated, single, myeloablative allogeneic cord blood transplants between 1995 and 2005 for treatment of hematologic malignancies. The patient age ranged from 12 to 55 years with 1 year survival at 37%. Cell dose less than 2.5×10^7, older age, advanced disease, positive cytomegalovirus status, female gender, and limited cord blood transplant center experience were associated with higher 100 day mortality. In addition, the German Red Cross, Mannheim Cord Blood Bank reviewed relevant aspects of cord blood selection and collection, testing, storage and processing of released frozen cord blood units for use [8]. This public cord blood bank was first established in 1996 and stores 1,750 cord blood units collected from seven hospitals from south-western Germany. From 1996 to 2009, data were available on 7,921 collected samples and 2,014 were accepted for long-term storage for transplantation use. Of these samples, 36 have been used for transplant purposes with 62% of the recipients being children under 15 years of age, but with a mean age of 20 years. Most patients receiving cord blood for transplants suffered from hematological disorders primarily acute leukemias (n=27) and the remaining blood units were used for treating immune deficiencies (e.g., severe combined immunodeficiency) or metabolic diseases (e.g., Hurler syndrome).

Eapen and colleagues in 2007 [4] reviewed the treatment of malignancies and cord blood transplantation in children with acute leukemia as an acceptable alternative to bone marrow. They reported on the outcomes of 503 children (<16 years of age) with acute leukemia and transplanted

with umbilical cord blood then compared with outcomes of 282 bone marrow recipients from the USA. Their study emphasized the paucity of data in the literature comparing transplantation using the two sources (cord blood vs bone marrow) specifically taking into consideration the HLA status of the donor and recipient. About 7% of their recipients of umbilical cord blood were transplanted with grafts that were HLA-matched and the remaining was mismatched for one or two antigens. The bone marrow recipients were either transplanted with grafts that were matched at the allele level for HLA-A, HLA-B, HLA-C, and HLA-DRB (41%) or mismatched (59%). In comparison with allele-matched bone marrow transplants, the 5 year survival in which the patient was leukemia-free, was similar to transplants of umbilical cord blood that was mismatched for either one or two HLA antigens. Their findings further supported the use of HLA-matched and/or one or two antigen HLA-mismatched for umbilical cord blood in treating children with acute leukemia requiring transplantation.

Later, Eapen and colleagues [12] compared leukemia-free survival in patients receiving cord blood, peripheral blood progenitor cells, or bone marrow transplantation in 1,525 patients older than 16 years treated for acute leukemia between 2002 and 2005. Cord blood transplantation results, 94% receiving one or two antigen mismatches, were comparable to 8 of 8 or 7 of 8 allele-matched peripheral blood or marrow transplantation. Transplant mortality was higher with cord blood but acute and chronic GvHD incidence was lower than in those receiving peripheral blood. Chronic GvHD was lower with cord blood than marrow transplantation. The investigators concluded that their data supported cord blood transplantation in adults when no HLA-matched unrelated donors are available for emergent transplantation situations.

Non-oncology

Frangoul et al. [2] reported their multicenter experience in the use of cord blood for non-oncology purposes in patients with primary immune deficiency (PID). They enrolled 364 adults and children in a study from 1999 to 2003 using an approved NIH sponsored protocol involving several sites and reported their results on 24 children with PID. They concluded that cord blood transplant has the potential advantage of more readily available donor samples that can be searched or accessed rapidly through international registries with a lower risk for viral contamination or other infectious agents in screened cord blood specimens, and with lower risks for graft versus host disease permitting less stringent HLA matching.

The median age in their study was 1 year (range of 0.2 to 7.8 years) and a median weight of 10.5 kg for the 24 children with transplants and PID receiving unrelated cord blood units. All patients received fully ablative conditioning regimen with identical graft versus host disease prophylaxis and supportive care. Neutrophil engraftment by day 42 was 58% with a probability of survival at 180 days of 67% and 63% at 1 year. Nine of their 24 children experienced graft failure and three patients died. They proposed that unrelated cord blood transplants should be considered for children with PID.

A separate survey by Prasad et al. [3] in 2008 summarized the outcomes of 159 young patients (median age of 1.5 years) with inherited metabolic disorders undergoing unrelated donor umbilical cord blood transplantation. Inherited metabolic disorders, particularly lysosomal and peroxisomal storage diseases are known to have progressive organ failure and early death [38]. In the past 25 years, nearly a thousand patients with metabolic storage disorders have received allogeneic hematopoietic stem cell transplantation for curative purposes using bone marrow from HLA—matched or mismatched related donors. This results in clinical benefit by replacing the missing enzyme produced by the donor cells circulating in the blood [39–43].

Previous experience with bone marrow transplantation can also be compared with cord blood transplantation for investigative purposes in non-oncology use. For example, Prasad et al. [3] reported on partially HLA-mismatched unrelated donor umbilical cord blood used for patients receiving myeloablative chemotherapy and cyclosporine-based prophylaxis. They studied the impact of patient characteristics, graft versus host disease, and clinical outcomes and followed the patients for a median time interval of 4.2 years. Unrelated cord blood units were selected from eight USA public banks for transplantation with at least three of six HLA loci in common in their survey. For the 159 children in their report, the top five metabolic diseases were: Hurler syndrome (n=45 patients); Krabbe disease (n=36); Sanfilippo syndrome (n=19); metachromatic leukodystrophy (n=15); and adrenoleukodystrophy (n=13). All grafted patients, except three, achieved donor chimerism of greater than 90% and all but four engrafted patients achieved and sustained normal enzyme levels relating to each specific metabolic disease when measurable in the blood. Their 1 year probability of overall survival in Hurler syndrome was 77%, Krabbe disease (74%), Sanflippo syndrome (79%), metachromatic leukodystrophy (65%) and adrenoleukodystrophy (77%). As anticipated, the children who underwent transplantation as newborns had better functional outcomes than those with progressive symptoms of the disease.

Lastly, Bizzetto et al. [9] reported in 2011 on 64 patients with hereditary bone marrow failure syndromes receiving cord blood transplants from related and unrelated donors.

By 60 days, 95% of related cord blood transplants achieved neutrophil engraftment. All but one received HLA-matched sibling grafts. Two of the 20 receiving related grafts developed Grade II–IV acute GvHD and the 2 year incidence of chronic GvHD was 11%. Three year survival was 95%. Among those receiving unrelated cord blood transplants, 86% received HLA-mismatched grafts. Neutrophil recovery at day 60 occurred in 55%. Grade II–IV acute GvHD occurred in 24% by day 100 and the 2 year incidence of chronic GvHD was 53%. Overall survival at 3 years was 61%.

Cord blood derived stem cells and regenerative medicine

According to Noverette and Contreras [22] approximately 10,000 patients worldwide, representing dozens of diseases including malignancies, bone marrow failure, hemoglobinopathies, inborn errors of metabolism and genetic or immune disorders have now received transplants using umbilical cord blood since Gluckman and others conducted the first cord blood transplantation for Fanconi anemia in 1988 [18]. Cord blood stem cells have shown the potential to be transformed into differentiated cell types when treated in specialized cell culture conditions and can produce organ-specific tissue. In addition to hematopoietic stem cells, cord blood contains endothelial cells, mesenchymal stromal cells, T-regulatory cells, dendritic cells, and natural killer cells [44]. These cell types can become an important area to study in medicine allowing for potentially new treatment options for additional diseases or conditions [45] including brain injury [46–48], strokes [47, 49–51], Parkinson's [52], Alzheimer's [50, 53], Huntington's [54] and amyotrophic lateral sclerosis [50, 55]. Other diseases in early stages of investigation include liver disorders [56], diabetes [57, 58], and myocardial infarction [49, 59]. Therapeutic targets for stem cells from cord blood include orthopedic applications for cartilage repair, spinal fusion and regenerative medicine [27, 44, 60, 61]. To date, it is unclear if therapeutic efficacy relates to injured or pathologic cell replacement, growth factor and cytokine release from infused cells, or stimulation/regeneration of host stem cells.

Conclusion

The protocols and standards for screening collections and storage of cord blood have now been established worldwide for both public and private (family) cord blood banks. Public banks are now part of registries for general search access for donor sources. Comparison of clinical outcomes and treatments of oncology and non-oncology diseases are available for access and reported worldwide. Thus, the technology has evolved from an experimental entity to an important medical alternative both in pediatric and adult hematopoietic transplantations. However, if the cord blood from an infant donor has an inherited hematologic, immunologic, or genetic disorder, then cord blood may not be used to expect a cure for the same disease in the same recipient. Therefore, families with recognized genetic diseases should be made aware of these issues, but cord blood banking may provide options for future treatment not currently recognized or in use for gene therapy approaches under development (e.g., ex vivo gene transfer method) and for the emerging field of regenerative medicine [19].

Advances in umbilical cord blood therapeutics show significant progress since the first transplant in 1988 involving a patient with Fanconi anemia. Allogeneic and private cord blood banks currently store more than 1,000,000 units worldwide with greater than 25,000 transplants reported. Cord blood as an alternative source of stem cells can provide several important advantages including the absence of risks for donors, availability for immediate access and use, minimal cell manipulation and reduced ethical issues raised by the general public.

The use of cord blood provides viable options for pediatric and adult patients with malignant conditions, hemoglobinopathies, metabolic disorders, immune deficiencies and regenerative applications. Additional updated information relating to cord blood banking and potential future transplantation and applications can be obtained through computer searched websites and protocol updates [31, 62, 63].

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