Special Articles

Clinical Use of Cord Blood for Stem Cell Transplantation

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Allogeneic bone marrow transplantations (BMT) from HLA-matched siblings have been successfully used for treatment of patients with high-risk hematological malignancies, genetic immunodeficiencies, metabolic disorders, or marrow failure syndromes. Unfortunately, most of patients lack matched related donors. Over the past decade clinicians have explored the suitability of umbilical cord blood (CB) as an alternative source for hematopoietic stem cell transplantation. Since the first related cord blood transplantation (CBT) was performed successfully for a child with Fanconi Anemia in 1988, there have been many children undergoing CBT from related donors. The further experience suggests that CB donation is a safe procedure for both mother and newborn. Subsequently, several quality CB banks were established worldwide with requirement of specific issues including donor recruitment, CB collection and processing, histocompatibility testing, infectious and genetic disease testing, transportation of CB, and protection of confidentiality of donors and recipients. The clinical data showed that unrelated donor CBT had comparable survival results to unrelated donor BMT. CB offers many potential advantages such as it is readily available, its collection causes no harm to the donor, and minimal HLA-disparity is acceptable. However, there are some disadvantages due to the volume and cell dose of each collected CB is limited, thus methods to enhance the number or quality of stem cells in CB are needed. At present the world's experiences suggest that CB is an acceptable alternative to bone marrow.

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Bone marrow transplantation (BMT) from human leukocyte antigen (HLA)-matched related donors has been successfully used for the treatment of children and adults with a high risk of recurrent hematological malignancies, genetic immunodeficiencies, metabolic disorders, or bone marrow failure syndromes. Unfortunately, the majority of patients who could potentially benefit from allogeneic BMT do not have suitably matched related donors. Despite the success of the National Marrow Donor Program (NMDP)[1,2] which was established in 1986, suitable HLA-compatible bone marrow and peripheral blood stem cell donors cannot be identified for all patients in need of allogeneic transplantation[3]. Therefore, over the past decade clinical investigators have explored the suitability of umbilical cord blood (CB) hematopoietic stem cells as an alternative source of hematopoietic stem cells (HSCs). While prospective clinical trials are still in progress, the world's experiences now suggest that CB is an acceptable alternative to bone marrow (BM).

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History of CB transplantation

The potential use of umbilical CB as a source of HSCs was proposed in 1982 by Edward A. Boyse, Hal E. Broxmeyer and Judith Bard. Subsequently a number of in vitro studies with human CB and in vivo studies with mouse blood were performed to document the feasibility of this proposal[4,5]. These early studies assessed whether previously untrained obstetrical health care professionals were able to collect CB that was free of bacterial and fungal contamination, determine the range and average volume of CB collected, and assay samples for the total number of nucleated cells and hematopoietic progenitor cells using in vitro culture methods following overnight shipment of CB units. During the course of these experiments, a number of CB units were cryopreserved and stored in liquid nitrogen freezers for potential clinical use. These studies were followed by experiments in which lethally

irradiated mice received transplantations of blood from near-term or term donors. Since it is impossible to get CB cells from mice because of the small size of the placenta and CB, the closest one can get to study of CB cells in mice is to use the blood of near-term and term mice which would be equivalent to the blood found in the cord. It was demonstrated that the blood of near-term and term mice contained sufficient numbers of HSCs capable of reconstituting hematopoiesis[5].

The first CB hematopoietic stem cell transplantation (CB-SCT) was performed for a 5-year-old child with Fanconi Anemia by Gluckman and colleagues in October 1988[6]. CB from the patient's HLA-identical sibling was collected in Durham, NC, by Gordon Douglas, than at the New York University Medical Center in New York; it was then shipped to Indiana University where it was cryopreserved by Broxmeyer's laboratory and then hand-delivered to Paris where the patient underwent his preparative regimen and CB-SCT[6]. The patient had durable engraftment of donor hematopoiesis and survived without hematological manifestations of the treated disease. Since then there have been many children with leukemia or bone marrow failure received myeloablative conditioning regimens for CB-SCT from related donors[6-9].

Following these first, largely successful transplant procedures, CB as an alternative source of HSCs was utilized by others and these transplantations were initially reported by an International Cord Blood Transplant Registry (ICBTR)[10]. It is now estimated that more than 80,000 CB units have been banked with at least 2,000 CB-SCT performed worldwide[11-14]. CB has now been utilized as a stem cell source for numerous malignant and nonmalignant diseases.

CB collection

CB can be collected for several purposes[15]. Public (not-for-profit) CB banks collect CB for the allogeneic transplantation of any recipient for whom the CB unit is a suitable HLA-match. CB can be collected and stored by expectant parents for potential use by the newborn infant, in terms of autologous transplantation, or a family member in need of a stem cell transplantation procedure, in terms of directed allogeneic transplantation. A number of techniques have been proposed for the optimal collection of CB. An optimal collection is generally considered to be a CB unit with sufficient volume of blood, total nucleated cells, and CD34+ cells. In addition, the unit would contain a low number of maternal T cells[16] and would be free of transmissible infectious agents.

As engraftment is closely correlated with the number of infused cells[14], numerous variables in the CB collection process have been examined in attempts to maximize the cell dose. Factors that may increase these numbers include volume of CB collected, number of nucleated cells or number of CD34+ cells, larger birth weight, fewer prior live births and birth order with a larger number of cells in first-born children[17]. Other factors that appear to increase cell dose include prolonged stress during delivery, placing the infant on the mother's abdomen after delivery[18], collection prior to delivery of the placenta, cesarean section[19,20], early clamping of the umbilical cord[18] and normal saline flush of the umbilical vessels[20,21]. In addition, there is a direct correlation of gestational age with nucleated cell count, but an inverse relation to CD34+ cell counts[17,22]. Factors that do not appear to effect the number of collected cells include maternal age, race and sex[23,24]. Despite this information, there remains considerable debate about the optimal collection method, with no consensus about the most appropriate process. While there appears to be little clinical impact on the newborn infant or the mother with these different techniques, the American College of Obstetrics and Gynecology[25] and the American Academy of Pediatrics[26] have strongly recommended that standard obstetric procedures not be altered to facilitate CB collections.

CB for public allogeneic use is generally collected at a limited number of sites in a single geographic location, with dedicated, trained personnel performing the collections according to standard operating procedures established by the CB bank[27]. These collection sites generally perform collections on only term infants. For directed allogeneic or autologous use, CB is generally collected at the birth location by local obstetrical care providers. The CB unit is then shipped to the CB bank for cryoperservation.

Despite these variable methodologies, the cellular characteristics of CB units are reasonably constant and distinct from BM and mobilized peripheral blood. Single CB units generally contain a 10-fold smaller dose of nucleated cells and CD34+ cells than that typically transplanted with BM or mobilized peripheral blood[17]. However, these units are enriched in hematopoietic progenitor cells[4].

Despite efforts to bank as many CB units as possible, it has been shown that a very large percentage of potential CB donors are ineligible for donation to public cord blood banks[28,29]. Chief reasons for not using potential CB donors is the presence of sexually

transmitted diseases in the mother, maternal fever during delivery, medications administered to the mother, maternal diseases, complications of delivery, presence of infections and problems with the placenta or umbilical cord. This high deferral rate of donors must be taken into account as the costs associated with CB collection and banking, are considerable.

Given the uncertainty about the optimal method of CB collection that results in the best quality CB product, but also preserves the health of the newborn infant and maternal donor, some CB collection programs and banks have instituted outcomes programs to evaluate the mother and baby after CB donation[29]. While diseases in the baby have on rare occasions been identified, resulting in the discarding of their CB units from public bank, the overall experience suggests that CB donation is a safe procedure for both mother and newborn.

CB Banking

The first CB bank was created at the Indiana University School of Medicine, with the first CB-SCT performed using units cryopreserved and stored in this bank[4,5]. As a result of the interest in CB transplantation generated from this pilot transplant experience, CB banks were established in 1993 in New York City, USA, in Dusseldorf, Germany, and in Milan, Italy. Subsequently, CB banks have been created worldwide in Austria, Belgium, Canada, China, United Kingdom, Finland, France, Germany, Ireland, Italy, Japan, Korea, the Netherlands, Poland, Singapore, Spain, Switzerland, Thailand and throughout the USA[13,27,30-35]. It is estimated that more than 80,000 CB units have been collected, tested and cryopreserved by these banks[13]. CB banking is a very complex and expensive process. The establishment of a quality CB bank requires attention to a number of specific issues including donor recruitment, donor consent, donor evaluation, labeling, CB collection, CB processing (e.g. red-cell depletion, volume reduction and stem cell selection) cryopreservation, histocompatibility testing, infectious disease testing, genetic disease testing, confirmation of recipient histocompatibility testing, tracking and allocation methods, transportation of CB from the collection site to the bank, transportation from the CB bank to the transplant center, thawing methods and protection of confidentiality of donors and recipients[13,36]. Therefore, a number of organizations have created standards to ensure the quality of CB banks and CB units, including the American Association of Blood Bank (AABB), the American Red Cross (ARC), the Cord Blood Transplantation Study (COBLT) of the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH), the European Group for Blood and Marrow Transplantation (EBMT), EUROCORD/NETCORD, the Foundation for the Accreditation of Cellular Therapy (FACT), the Group for the Collection and Expansion of Hematopoietic Cells (GRACE), the International Society for Cellular Therapy (ISCT) and the NMDP[13].

CB units that are banked for allogeneic transplantation undergo histocompatibility typing using conventional serological and molecular, DNA based techniques for class I antigens and molecular HLA typing for class II alleles. Because of the limited amount of CB for HLA typing and infectious disease testing, molecular methods, including the polymerase chain reaction (PCR) and sequence-specific oligonucleotide probe (SSOP) methods, are used to better define class I and class II alleles while using very small amounts of CB cells[37]. While these molecular techniques better define specific alleles, the optimal level of HLA typing for CB and the clinical impact of higher degrees of resolution are not currently known.

In addition to ABO, rhesus and HLA typing, CB banked for transplantation is tested for infectious agents in accordance with the requirements and recommendations of regulatory organizations as mentioned above. Specifically, CB units and the mother's blood are routinely tested for hepatitis B and C, human immunodeficiency virus (HIV), human T-cell lymphotropic virus (HTLV), cytomegalovirus (CMV) and syphilis[30,31,38].

Since some infectious agents can be transferred in liquid nitrogen, newly collected CB units are typically kept in quarantine until infectious disease testing is complete. If they are found to be free of potentially transmissible infectious agents, the units are placed into long-term liquid nitrogen storage. In addition to this testing, CB banks also elicit a history of genetic diseases in the family, travel of donors to places that have a high frequency of transmissible infections and other high-risk behavior, including intravenous drug used and high risk sexual behavior, upon which CB units may be excluded from the bank. These screening questions are similar to these used for blood donor screening by the AABB.

It is currently unclear how long CB can be viably cryopreserved, although theoretically this should be for at least the life time of an individual. It has been shown that upon thawing, units of CB that were cryopreserved for up to 15 years contained 83$\pm$12%

of nucleated cells with 85±25% recovery of multipotential progenitor cell values[39] essentially equal to 10 years defrost[40]. Moreover, the proliferative capacities of these early progenitor cells were intact for colonies forming and high self-renewal potential. Most importantly, CD34+ cells separated from the 15 years defrosts were able to multi-lineage engraft sublethally irradiated non-obese diabetic with severe combined immunodeficiency syndrome (NOD/SCID) mice, suggesting high-quality recovery of HSCs[39]. Laboratory studies demonstrated that CB cells frozen for several years can be thawed, gene transduced and ex vivo expanded[39,41].

The unique paradigm created by CB banking has raised a number of ethical, regulatory and legal issues, including questions about recruitment, confidentiality, ownership, informed consent and fairness in the allocation of this valuable resource. Considerable efforts have been made to define these issues to ensure the appropriate operation of CB banks[36,42,43].

Searching for a CB donor

Several potential advantages of unrelated donor CB transplantation over unrelated donor BM or mobilized PB is the ready availability of banked CB units, a shorter time to acquisition of CB with a more rapid time to transplantation and the ability to tolerate greater degrees of HLA disparity. A recent analysis of the NMDP suggest that if 4 out of 6 and 3 out of 6 antigen matches are clinically acceptable, donors would be identified 99% of the time for patients of all races[44]. The clinical experience with CB suggests that HLA mismatches of up to 3 antigens result in acceptable clinical outcome. Thus, the availability of a suitable number of CB units would allow for the transplantation of the majority of patients. Based upon traditional search methods and strategies, several groups have demonstrated that the time required for identification of a suitable stem cell source and the time to transplantation is more rapid for unrelated donor CB than for unrelated donor BM[45,46]. This shortened time interval may be as long as 4 weeks.

Finally, the ability to safely and effectively perform pre-implantation genetic diagnosis, histocompatibility testing and in vitro fertilization allow parents with children with diseases in need of transplantation the option of creating a suitable CB donor. While the ethical issues involved in this process continue to be debated, the advent of this technology will undoubtedly have a tremendous impact upon the practice of clinical transplantation.

Clinical results

While there is now extensive clinical experience for the transplantation of related and unrelated cord blood, to date, there are no prospective, randomized clinical trials or retrospective cohort control studies comparing CB to BM or mobilized PB. The vast majority of clinical reports to date represent descriptive, retrospective case series of patients.

Related donor CB transplantation

The large case series of related donor CB-SCT have been reported by the International Bone Marrow Transplant Registry (IBMTR)[47] and EUROCORD[48]. These retrospective series have shown survival rates of approximately 60% at 1 year. There is a report in a retrospective cohort controlled analysis of children less than 15 years of age transplanted with HLA-identical CB or BM[48]. In this study, 2052 unmanipulated BM recipients were compared to 113 CB recipients. Transplants were performed between 1990 and 1997 at 207 transplant centers worldwide. The median period of follow-up was 27 months (range: 3-85). This study demonstrated a lower risk of acute and chronic GVHD with CB, a slower rate of neutrophil and platelet recovery in the first month post-transplant with CB, but similar survival in both CB and BM recipients. These findings support the use of HLA-matched related donor CB as an acceptable alternate to BM for children with HLA-identical siblings.

Unrelated donor CB transplantation

The vast majority of the experience with unrelated donor CB-SCT is the result of retrospective case reports of patients[14,47-50], rather than the results of prospective clinical trials[51]. The largest of these retrospective series has been recently updated[50]. The large series of 861 patients reports the outcome of unrelated donor CB transplantation as facilitated by the New York Cord Blood Program. The retrospective analyses[14,46,52] suggest that unrelated donor CB, T-cell depleted unrelated donor BM and unmanipulated BM have different risks and potential advantages, with similar overall survival. The data support the overall findings suggesting that unrelated donor CB is a reasonable stem cell source for children without a matched related donor, giving comparable survival results to unrelated donor BM.

CB transplantation in adults

As a result of the limited number of cells available in the finite volume of collected CB, there was

initial concern that CB may not contain a sufficient number of cells to reliably engraft larger children, adolescents and adults. However, with the growth of CB banks and improvements in CB collection techniques, CB units with a large number of nucleated cells are becoming increasingly available. As a result, while there are still no prospective clinical trials in adults, there is an emerging experience for CB transplantation in adults[12,13,53-55]. The experience suggests that the probability of engraftment and incidence of acute and chronic GVHD are tolerable, but non-relapse mortality is high. While this may be the result of performing CB-SCT in only high risk patients (e.g. hematologic malignancies, marrow failure syndrome), prospective studies and case controlled comparisons of CB to BM in adults are required to better define the use of CB in adults.

Experience of unrelated donor CB transplantation in Thailand

There was a first ever report from Vanichsetakul et al[56,57] of 3 children undergoing Thai unrelated donor CB-SCT facilitated by National cord blood bank, National blood centre, Thai Red Cross Society. The patients were diagnosed Wiskott-Aldrich syndrome (1) and Beta-thalassemia/ hemoglobin E (2). All achieved successfully donor engraftments with 2 cases complicated by acute GVHD that responded well with immunosuppressive therapy.

Future directions for clinical CB transplantation

Slower neutrophil and platelet engraftments, as well as a lower probability of engraftment compared to other graft sources, have been consistently reported in children and adults following CB-SCT. Several strategies have been explored to address this problem. The expansion of CB banks with an increasingly large number of CB units with a larger cell dose is making larger CB units more available for transplantation. One approach for facilitation of neutrophil and platelet engraftment is the ex vivo expansion of CB prior to transplantation[58]. In the largest series to date 25 adults and 12 children with malignancies received the infusion of CB expanded in G-CSF, megakaryocyte growth and development factor and stem cell factor. With a median follow-up of 30 months, 35% of patients survive. Future studies will continue to explore the safety and efficacy of ex vivo expansion and different expansion conditions. Finally, the pooling of two or more CB units from different donors is now being explored. However, the safety and efficacy of this approach is currently unknown. The initial report of this approach[59] involved the transplantation of two units of CB into an 84-kg adult recipient. Neutrophil engraftment occurred on day 25 with both units contributing to blood production. Whether engraftment by both, one or none of the units are maintained remains to be determined. The prospective use of multiple CB units is currently ongoing.

Conclusion

The experience with CB-SCT is extremely encouraging. CB offers a number of potential advantages as an alternative source of HSC. Specifically, CB is readily available and appears to present no risk to the donor. As allogeneic CB banks reach sufficient size, the time required to acquire a donor unit may decrease further, allowing transplantation to occur at an earlier time. Finally, due to the vast amount of CB continually available for banking, it may be possible to bank only CB units negative for all the viruses for which screening tests are currently available. Nevertheless, there are several disadvantages. Since the volume of each collected CB is limited, methods to enhance the number or quality of HSCs in CB are needed. In fact, a problem with ex vivo expanded cells may be their loss of effective homing capacity. In the unrelated CB setting, it is impossible to reacquire CB from the donor when recipient experiences graft failure or relapse. Ex vivo expanded cells stored for future use or the use of another stored CB unit may circumvent these possible problems. In summary, there are a number of medical, scientific, technical, ethical and regulatory challenges in the era of CB transplantation. True potential advantages and disadvantages of CB HSCs should emerge as experience in this still relatively new field continues.

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การใช้เลือดจากสายสะดือในทางคลินิกเพื่อปลูกถ่ายเซลล์ต้นกำเนิดเม็ดโลหิต

ปรีดา วาณิชยเศรษฐกุล

การปลูกถ่ายไขกระดูกแบบ allogeneic จากพี่น้องที่มีหมู่เนื้อเยื่อ HLA ตรงกัน สามารถประสบความสำเร็จในการรักษาผู้ป่วยโรคมะเร็งทางโลหิตวิทยาที่มีความเสี่ยงสูง โรคภูมิคุ้มกันบกพร่องจากพันธุกรรม โรคเมตาบอลิคผิดปรกติ และกลุ่มโรคไขกระดูกบกพร่องหรือผิดปรกติ โชคร้ายที่ผู้ป่วยส่วนใหญ่ไม่มีพี่น้องหรือญาติที่มีหมู่เนื้อเยื่อตรงกัน เป็นเวลากว่าทศวรรษที่ผ่านมา ที่วงการแพทย์พยายามศึกษาความเหมาะสมของเลือดจากสายสะดือเพื่อใช้เป็นแหล่งทางเลือกสำหรับการปลูกถ่ายเซลล์ต้นกำเนิดเม็ดโลหิต ตั้งแต่มีการปลูกถ่ายเลือดจากสายสะดือสำเร็จเป็นครั้งแรกในผู้ป่วยเด็กโรคโลหิตจาง Fanconi เมื่อปี ค.ศ. 1988โดยผู้บริจาคคือน้องผู้ป่วย ก็มีผู้ป่วยเด็กหลายรายได้รับการปลูกถ่ายเลือดจากสายสะดือของน้อง จากประสบการณ์พบว่า การบริจาคเลือดจากสายสะดือเป็นวิธีการที่ปลอดภัยต่อตัวทารกแรกเกิดและมารดาที่คลอด ต่อมา มีการจัดตั้งธนาคารเลือดจากสายสะดือและรกที่มีคุณภาพทั่วโลก โดยต้องได้มาตรฐานทั้งในด้านการคัดสรรผู้บริจาค การเก็บและกระบวนการในการสงวนรักษาการตรวจหมู่เนื้อเยื่อและการเข้ากันได้ การตรวจคัดกรองโรคติดเชื้อและโรคที่ถ่ายทอดทางพันธุกรรม การขนส่งเคลื่อนย้ายถุงเลือดจากสายสะดือ และการปกปิดข้อมูลเป็นความลับของทั้งฝ่ายผู้บริจาคและฝ่ายผู้ป่วย จากข้อมูลทางคลินิกพบว่า การปลูกถ่ายเลือดจากสายสะดือของอาสาสมัครผู้บริจาคได้ผลการรักษาและการมีชีวิตรอดดี ทัดเทียมกับผลการปลูกถ่ายไขกระดูกจากอาสาสมัคร เลือดจากสายสะดือมีข้อดีหลายอย่าง อาทิ การมีพร้อมให้ใช้ได้ทันทีถ้าถูกเก็บอยู่ในธนาคารไว้แล้ว ขั้นตอนการเก็บไม่มีอันตรายต่อทารกแรกเกิด และการมีหมู่เนื้อเยื่อ HLA ต่างจากผู้ป่วยเพียงเล็กน้อยก็ยังใช้ปลูกถ่ายได้ผล อย่างไรก็ตาม เลือดจากสายสะดือมีข้อเสียบ้าง เช่น ปริมาณเลือดและเซลล์ที่เก็บได้แต่ละครั้งมีจำนวนจำกัด อาจไม่เพียงพอที่จะใช้ในผู้ป่วยน้ำหนักตัวมาก ดังนั้น จึงต้องมีการพัฒนาหาวิธีการเพิ่มจำนวนเซลล์ต้นกำเนิดและคุณภาพของเลือดจากสายสะดือต่อไป ปัจจุบันประสบการณ์ทางการแพทย์ทั่วโลกยอมรับว่า เลือดจากสายสะดือเป็นทางเลือกของเซลล์ที่จะปลูกถ่ายแทนไขกระดูกได้