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ASBMT Committee Report

Collection and Preservation of Cord Blood for Personal Use

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ABSTRACT

Unrelated-donor umbilical cord blood (CB) is a useful alternative hematopoietic stem cell source for patients without suitably matched and readily available related or unrelated stem cell donors. Expectant parents today may have the option of either donating the CB to a public CB bank or keeping and storing the CB in a private bank for potential use in the future. The alternatives are often referred to as public banking and private banking. On behalf of the American Society of Blood and Marrow Transplantation (ASBMT), we have reviewed the currently available data and opinions and offer the following recommendations:

1. **Public donation of CB is encouraged where possible.**
2. **The probability of using one's own CB is very small—difficult to quantify but probably as low as 0.04% (1:2500) to 0.0005% (1:200,000) in the first 20 years of life—and therefore, storage of CB for personal use is not recommended.**
3. **Family member banking (collecting and storing CB for a family member) is recommended when there is a sibling with a disease that may be treated successfully with allogeneic transplant. Family member banking on behalf of a parent with a disease that may be treated successfully with allogeneic transplant is only recommended when there are shared HLA-antigens between the parents.**

The committee acknowledges the expanding potential of indications for CB in the future, and suggests review of these recommendations at regular intervals.

KEY WORDS

Cord blood • Personal storage

INTRODUCTION

In the 18 years since the first umbilical cord blood (CB) transplant was reported in the *New England Journal of Medicine*, the fields of CB research, banking, and transplantation have flourished. CB transplantation has been used to successfully treat leukemia, lymphoma, myelodysplasia, aplastic anemia (AA), hemoglobinopathies, metabolic storage diseases, and immunodeficiencies [1]. There are >250,000 CB units stored in public CB banks for unrelated use, and >8000 CB transplants have been performed [2]. Expectant parents today may have the option of either donating the CB unit to a public CB bank or keeping and storing the CB in a private bank for potential use in the future. In this report, we review stem cell transplantation using unrelated-donor CB, family member (directed donor) CB, and autologous CB, using the patient's own stored CB. We touch briefly on potential additional uses of CB and how these may influence future recommendations. Finally, we state an opinion on personal storage of CB. A summary in lay terms for expectant parents is included at the end of the report.

OVERVIEW OF UNRELATED-DONOR CB TRANSPLANTATION

Human CB is one potential source of hematopoietic stem cells (HSC) that is capable of reconstituting hematopoiesis after myeloablative or nonmyeloablative therapy [2]. Multiple studies in patients with hematologic malignancies have demonstrated that cryopreserved CB from 4-6/6 HLA-A, -B antigen, and -DRB1 allele matched unrelated donors contain sufficient numbers of HSC to achieve engraftment in most pediatric patients [1,2]. More recent data demonstrate promising results in larger children and adults, as well as patients with nonmalignant disorders [1-4]. Clinical experience has highlighted two chief benefits of unrelated donor CB. First, as a cryopreserved HSC source, CB is rapidly available with an absence of donor attrition, and has the advantage that a transplant can be scheduled according to patient needs rather than donor availability. Second, in comparison to adult HSC graft, the incidence of graft-versus-host disease (GVHD) is lower in unrelated CB transplants without the loss of a graft-versus-malignancy effect [5].

However, the low cell content of CB units may be its major limitation. Multiple studies have demonstrated the adverse effect of low cell dose upon engraftment, treatment-related mortality (TRM), and survival [1,2,6]. The limitation of cell dose contributed to the inferior hematopoietic recovery, increased TRM, and inferior survival of adult single unit CB transplant recipients (n = 169) compared to that of 6 of 6 matched unrelated volunteer bone marrow (BM) recipients (n = 367) reported by Laughlin et al [6]. Notably, disease-free survival (DFS) after CB transplant was comparable to that of HLA-mismatched BM recipients (n = 83), highlighting CB transplantation as a viable alternative to HLA-mismatched volunteer donors for adult recipients. In addition, a similar evaluation by Eurocord revealed comparable outcomes after unrelated donor BM and CB transplant in adults [7]. Finally, the use of double unit grafts as a strategy to augment graft cell dose has been associated with improved engraftment and reduced TRM compared to single-unit historic controls with a DFS at 1 year of 70% in patients transplanted in remission [3]. Furthermore, comparable results following CB transplant with reduced intensity (RIC) or nonmyeloablative conditioning regimens highlights the suitability of CB for patients unsuitable for ablative conditioning [4,8].

No randomized trials have compared transplantation using grafts from unrelated volunteer donors versus CB. However, a retrospective evaluation has recently compared the outcomes of 4-6 of 6 HLA-A, -B antigen, and -DRB1 allele-matched single-unit CB transplantation with those of 8 of 8 allele-matched unrelated volunteer donor transplants in children <16 years with leukemia [5]. In comparison to an 8 of 8 matched adult donor, the 5-year DFS after 6 of 6 matched CB transplant (n = 35) was superior. These results support the use of HLA-matched CB in preference to matched BM, or of mismatched CB if a unit of adequate cell dose is available for the treatment of children with leukemia.

In children, CB has been used to successfully treat young children with metabolic diseases, such as adrenoleukodystrophy and infantile Krabbe's disease [9,10]. Wider use of CB in adults is dependent on improvement in TRM compared with marrow or peripheral blood stem cell (PBSC) transplants. Thus, if engraftment can be improved, as has been seen with more recent experience using fludarabine (Flu)-based conditioning and/or double unit grafts, the argument in favor of CB in both adults and children will be even further strengthened because of the lesser incidence of chronic GVHD (cGVHD) and the likely consequent improvement in quality of life.

CB COLLECTION, PROCESSING, AND CRYOPRESERVATION

To provide suitable CB units for transplantation, banks have been developed to collect, process, and cryopreserve CB. There are 3 major kinds of CB collection and storage: (1) CB units that are donated for public use; (2) CB units that are collected from a healthy newborn and stored for another family member who suffers from a disease that is known to be treatable by HSC transplantation ("directed donor" CB collection), and (3) CB units that are collected from a healthy newborn and stored for a fee for private use in anticipation that the CB may someday be needed as therapy for autologous or family-member use.

There are two generally accepted methods for collecting CB following delivery of the newborn baby. One is to collect the blood immediately after delivery prior to placental separation from the wall of the uterus. The other way is to deliver the placenta with the cord clamped and pass it from the operative or delivery field to an attendant who performs the CB collection. Several studies have compared CB units collected by both techniques, and, in aggregate, they do not demonstrate consistent or significant differences in total blood volume, $CD34^+$ count, or total nucleated cell count between the methods [11]. The major issues in obtaining high-quality units for transplantation are maximizing the volume of blood collected, avoiding microbial contamination, and avoiding undue delays that could result in clotting of the specimen.

Optimal CB unit processing, cryopreservation, and storage are critical to ensuring the safety and potency of the graft. The most common technique involves sedimentation of CB red blood cells followed by

centrifugation of the leukocyte-rich plasma into a small volume that is mixed with a cryopreservative solution (typically DMSO), followed by controlled rate freezing and storage in liquid nitrogen. An alternative processing technique that is designed to minimize both handling during processing and nucleated cell loss involves volume reduction by a single centrifugation step and results in a CB product that contains nearly all of the original leukocytes and red blood cells prior to freezing. Early studies reported that stepwise postthaw CB dilution to decrease osmolality, followed by washing, was important to maintain CB progenitor cell viability and engraftment speed, but recent clinical studies show that postthaw CB dilution without washing, or even direct infusion of thawed CB, is associated with equally reliable engraftment and freedom from side effects [12].

CB for Family Use

Although there is less published literature on family-member CB transplantation, HLA-matched related-donor CB transplantation has been demonstrated to be an effective therapy for patients with hematopoietic disorders [13]. Eligibility determination of newborn donors and their mothers for family member medically indicated CB donation usually employ strict quality control criteria. However, less stringent eligibility criteria than is used for public CB donation may be appropriate in some instances. For example, a maternal history of hepatitis would disqualify donation to a public CB bank, but in related CB banking this exclusion would commonly be waived if the mother had negative testing for actively infectious hepatitis.

Most public unrelated-donor CB banks are organized to also support medically indicated CB collection and banking from related donors. In addition, the National Institutes of Health (NIH) has funded one CB bank with specific expertise in family banking, especially for children with hemoglobinpathies. This bank, the Children's Hospital Oakland Sibling Donor Cord Blood Program, is the largest publicly funded CB bank for the purpose of medically indicated family banking, and collects CB almost anywhere in the United States if the medical indication is appropriate. It currently stores >3000 CB units for specific potential transplant recipients who have accepted indications for transplant (49% for malignant conditions, 28% sickle cell disease, 6% thalassemia, 17% other nonmalignant). As of 2006, this CB bank had facilitated 65 identical sibling or related-donor transplants, 51 using CB as the sole source of the graft, 23 patients with MDS/acute leukemia, 21 with thalassemia, 12 with sickle cell disease, and 9 with other nonmalignant conditions [14,15]. Graft failure occurred in 3% of patients, and TRM was 6%. Overall survival (OS) and DFS rates at 16 months were 80% and 76%, respectively, and 93% and 88%, respectively, for those patients with nonmalignant conditions. These results confirm the feasibility and support the efficacy of sibling donor CB transplants for certain hematologic disorders, metabolic disorders, and other diseases. However, there is little experience with using a 3 of 6 matched CB unit stored for a parent.

In consideration of the above information and studies, family member (directed donor) CB banking can be recommended in the following situations:

1. A sibling of the expected child has a disease that can be successfully treated with hematopoietic stem cell transplantation (HSCT). Such diseases include leukemia, lymphoma, a hemoglobinopathy, and bone marrow (BM) failure syndrome.
2. The parent of the expected child has a disease that can be successfully treated with HSCT, and there are shared HLA antigens between the parents.

CB for Personal Use

The business of personal storage of CB has grown considerably, particularly in the United States. There are numerous private CB banks that charge a fee to collect and store CB for private use. The reasons for widespread private banking include: (1) parental interest in giving their children "biologic insurance" in case a disease develops in future years that can be treated with an autologous stem cell transplant, and (2) aggressive marketing by banks offering private collection and storage of CB. In addition, the economics of CB banking, which are extremely labor- and resource-intensive, have enabled a rapid expansion of private banking. A public bank recovers costs only when CB units are shipped for transplant, whereas a private bank receives immediate income when the CB unit is collected and ongoing annual income for maintenance of the stored unit.

Our committee conducted a telephone survey of private CB banks in the United States. Susan Stewart from our committee contacted medical or other representatives of 17 private CB banks, representing a combined inventory of approximately 460,000 units [16]. Eleven responded, including three with written responses. Survey questions included information on the number of CB units stored and the number of units provided for transplantation, the diseases transplanted, and whether the CB units were used for autologous or family-member transplant. Information on costs of collection and storage was not obtained. The responding banks reported a total of 99 units that have been shipped for transplantation. Two of the largest banks (Cord Blood Registry and Viacord) noted that the bulk of their collections have been in the past 5 years,

so the eventual disposition of the units cannot be known at this time. In addition, they suggested that medical uses for autologous CB units may expand in the future, making the units more useful.

There are little data available concerning the outcome of transplantation using privately banked CB units. However, there are a few case reports of personally stored CB units collected at birth that have been used for autologous transplantation in later life. The first such case, published in 1999, described a 14-month-old child with neuroblastoma, who had CB collected at birth because her brother had acute myelogeneous leukemia (AML) [17]. She received an autologous CB transplant and was alive and disease free 14 months after transplantation. Fruchtman and colleagues [18] reported on a successful autologous CB transplant for severe AA, following liver failure and liver transplantation. Two patients with severe idiopathic AA, developing at the ages of 5 and 9, respectively, were reported at the 2007 BMT Tandem Meetings [19]. Both patients are alive and well, with normal blood counts with a posttransplant follow-up of 8 and 3 months, respectively. Hayani and colleagues [20] have recently reported the first case of an autologous CB unit being used for the treatment of leukemia. A 3-year-old girl with acute lymphoblastic leukemia (ALL) with an isolated central nervous system (CNS) relapse received an autologous CB transplant using cryopreserved CB cells stored privately at her delivery. The patient is disease free 24 months after transplant.

The use of autologous CB for autoimmune disease is under preliminary investigation. Haller and colleagues [21] treated 7 children with type I diabetes with autologous CB infusion; these children had lower insulin requirements and hemoglobin A1c than a randomly selected population of severe diabetic children. The Cord Blood Registry reports that 11 autologous CB units have been used for transplant for indications including aplastic anemia, cerebral palsy, traumatic brain injury, and immune deficiency, but no outcome data have been published on these transplants.

Concerns about storage of CB for future autologous use include:

- *Probability of clinical need.* It is difficult to estimate the likelihood of use of an autologous CB unit collected at the birth of a healthy baby. Using the probability of developing cancer, the need for transplantation, and the lack of a matched allogeneic donor, estimates of the likely use of a stored autologous CB unit are imprecise but would appear to range from 1:2500 (0.04%) to 1:200,000 (0.0005%) [22-26]. Autologous transplant can be efficacious for patients with diseases such as lymphoma, myeloma, and neuroblastoma, and in many cases autologous marrow or peripheral blood is adequate, or an allogeneic HSC is preferred. However, patients with genetic marrow failure and immunodeficiency syndromes, metabolic storage diseases, and hemoglobinopathies who need a transplant require an allogeneic transplant and a donor [22]. Therefore, privately stored CB would be of no use for treating these diseases.
- *Latent disease.* The abnormal or diseased cells that cause disease later in life may be present in the patient's preserved CB, and may not be detectable. For example, investigators have found that leukemic blood cells are present in the neonatal blood of children later diagnosed with leukemia. In the report of Rowley et al [27], 3 children, aged 2, 5, and 6 with acute lymphoblastic leukemia and the chromosome translocation t(4;11), had their Guthrie cards (filters containing newborn blood) examined and were found to have the t(4;11) abnormal cells at birth. For these reasons, public banks discard CB units from their inventories if the donor is subsequently diagnosed with leukemia. There have been no published reports of CB grafts containing detectable leukemia cells, but the malignant cells may be below the level of routine detection.
- *Quality and viability.* The standards for public CB banking and for private CB banking may differ in terms of maternal eligibility and nucleated cell count requirements, and these factors may influence the overall quality of the stored CB. Long-term viability of personally banked CB cells is also a concern, as the CB cells collected at birth may not be used for many years. CB has been found to be viable 15 years after cryopreservation, but there are no data beyond this time point [28,29].
- *Graft-versus-leukemia (GVL) effect.* The high relapse rates after autologous or syngeneic transplants and the benefit of a GVL effect of an allogeneic transplant suggests that autologous CB would not be the optimal cell source for patients with leukemia needing a transplant.

In consideration of the above information and studies, the following recommendations are offered:

1. The expectant parents should be encouraged to donate their newborn's CB to a public bank when possible.
2. Expectant parents should be informed that, although private CB banking is available for purchase, the chance of personally stored CB being of benefit to their child is extremely low (about the same chance of maternal death during childbirth), and that current knowledge is limited as to the long-term CB viability and the likelihood of success of autologous CB transplantation.
3. Parents who nevertheless choose to store CB for personal use should be advised to carefully review their contract and financial responsibilities, and to

inquire about quality standards, median nucleated cell dose of stored units, and accreditation of the CB bank.

FUTURE NEED AND USES OF CB

Unrelated-donor CB as a public resource is likely to be of increasing importance in the future. CB may become the preferred HSC source for some patients, even those with allele level matched unrelated volunteer donors. Also, because the required HLA match is less stringent with CB than with unrelated volunteer donors, access to transplantation can be expanded to more racial and ethnic minorities that have a smaller pool of registered potential donors.

Already data suggest that 6 of 6 A, -B antigen, and -DRB1 allele-matched CB is superior to 8 of 8 allele matched-unrelated BM transplantation in children with leukemia, with 5 of 6 CB transplantation being comparable but with less GVHD [5]. If the CB inventory can be expanded such that the majority of patients would have at least 5 of 6 matched CB grafts of adequate size, CB may well outperform fully matched volunteer donors, or at least be comparable with less GVHD. This is of particular significance, given the increased use of peripheral blood unrelated volunteer grafts and the associated significant incidence of cGVHD. Expansion of the use of CB grafts in adult transplantation will be facilitated by development of reliable methods to diminish graft failure rates, enhance engraftment speed, and immune recovery, all without increasing GVHD. Further, the National Marrow Donor Program has documented that the genetic heterogeneity of the U.S. population is increasing (NMDP, 2007, personal communication). Therefore, the numbers of patients without suitably matched volunteer donors will likely increase, and will be further compounded as access to health care is improved for racial minorities. Finally, CB could be an HSC resource that is readily available in the event of a mass radiation accident or bioterrorism attack, rendering a large number of people to need transplant at short notice. For all of these reasons the ASBMT and the transplant community have strongly encouraged support of public CB banking and research initiatives toward the further development of this important resource for hematopoietic grafts.

Other potential uses for CB outside the field of oncology might include transplantation of nonhematopoietic stem cells that are present in CB (eg, mesenchymal stem cells and other as-yet unrecognized stem cell populations), or might take advantage of increased plasticity of CB stem cells and their ability to differentiate into alternative tissues such as endothelium, bone, cartilage, neural, or cardiac cells, or their ability to express transfected genes. Preclinical investigations have employed CB mononuclear cells in the therapy of neurologic disease (stroke, spinal cord, or brain trauma, amyotropic lateral sclerosis), cardiac disease (myocardial infarction or ischemia, cardiac injury, valve repair), and tissue repair [30-33]. Whether CB will eventually be useful in treating these diseases is unclear; the usefulness of privately banked CB for the treatment of nonhematopoietic and other diseases is unknown. It is possible, but not yet known, whether privately banked CB eventually might be used for treatment of nonmalignant conditions and have wider applications.

In summary, the uses of CB stored in public banks are likely to increase in future years; expanded use of CB stored for personal or family use is also possible. For the foreseeable future, however, the likely use of privately stored CB is exceeding small. Therefore, we recommend priority to public donation of CB whenever possible. However, emerging data should be reviewed, and these recommendations should be assessed periodically.

RECOMMENDATIONS OF OTHER ORGANIZATIONS

Our committee has reviewed the findings and conclusions of other organizations that have studied these issues, including those in the fields of pediatrics and obstetrics and international medical organizations and government agencies. There is overwhelmingly consistency in their conclusions about current and future uses of CB.

Pediatrics and Obstetrics

Prospective parents aware of the availability of pubic and private CB storage frequently ask their obstetrician or pediatrician for advice about the alternatives. To assist their members to respond to these queries, both the American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics (AAP) have prepared formal position statements [34,35]. Both medical associations strongly encourage parents to donate their children's CB to public banks if those opportunities are available in their geographic area. They also encourage parents to consider directed donor storage if there is a first degree relative with a disease or disorder that is known to be treatable by CB transplantation. Both organizations discourage parents from purchasing private storage for CB as "biologic insurance" against the possibility that their child might some day need the CB back for transplantation.

Both organizations express serious concerns about the tactics that some banks use to market private storage to expectant parents who have relatively short time to investigate the issues and make an informed decision. These tactics often include exaggerated claims about the lifetime vulnerability of the newborn child, the benefit of having stored CB, and their obligations

as responsible and caring parents. Both organizations endorse informed consent prior to arrival in the labor and delivery suite, testing of units for infectious diseases, and disclosure of test information to parents. Finally, the AAP recommends that, if a physician or nurse is compensated in any way to counsel or recruit parents to privately bank their newborn's CB, that fact should be disclosed to the parent.

International

Several organizations in Europe have published position statements on CB storage for personal use. Worldwide, there are approximately 134 private banks with an estimated 780,000 CB units stored [36]. The European Union's position states, "The possibility of using one's own cord blood stem cells for regenerative medicine is currently purely hypothetic. Research in this field is only at a very early stage … the legitimacy of commercial cord blood banks for autologous use should be questioned as they sell a service that has presently no real use regarding therapeutic options" [37].

In Italy and France, the sale of CB collection and storage services for personal use is illegal. In Spain it is permitted by law.

CONCLUSIONS

Since the first report of a successful CB transplant almost 20 years ago, the uses of CB have expanded rapidly and CB banking has flourished.

The chance of a CB unit being released for transplant from a public bank is at least 100 times greater than that of a privately banked unit. Yet, the number of CB units privately stored for personal or family use is currently 3 times greater than the number of units in public banks. CB is a valuable community resource, and expectant parents should be educated to make informed decisions about its uses. To assist expectant parents in making an informed decision, the committee has prepared a summary of its findings, conclusions, and recommendations in lay terms using a question-and-answer format (see Appendix).

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APPENDIX: SHOULD YOU STORE YOUR BABY'S UMBILICAL CORD BLOOD? SOME FACTS TO HELP GUIDE YOUR DECISION

Why Collect Umbilical Cord Blood?

In recent years, doctors have successfully treated patients with life-threatening diseases, such as leukemia, by transplanting them with blood collected from the umbilical cord of a healthy baby. This new treatment, called cord blood transplantation, has prompted many expectant parents to consider storing their newborn's umbilical cord blood for possible future use.

Can I Collect and Store Cord Blood for My Own Baby in Case It's Needed?

Yes, but the chance of using one's own cord blood is very low—currently less than 4/100th of 1%. Many patients who need a cord blood transplant need cells from a donor, not their own blood cells, to cure their disease. Their own cord blood may carry the same cells that caused their disease. Frequently, brothers and sisters are the best match as donors. Otherwise, public registries such as the National Marrow Donor Program can find unrelated cord blood or adult volunteer donors for many people who need a transplant.

Can My Baby's Cord Blood Help a Family Member or Friend?

If the baby has a brother or sister with a disease that can be treated by a cord blood transplant, banking the baby's cord blood can make sense, and may be recommended by your doctor. For such families, the Children's Hospital Oakland Sibling Donor Cord Blood Program (CHORI) specializes in banking cord blood at no charge. Several public cord blood banks also bank cord blood for families who have an identified need for the cells.

Collecting and keeping a baby's cord blood may be recommended if the baby's parent has a disease that can be treated by transplant, both parents share genetic markers called HLA antigens, and if a better donor is not available. Banking cord blood for family members other than the baby's siblings or biologic parents is not advised without the doctor's guidance, because it is unlikely that the cord blood unit will be useful.

Can I Donate My Baby's Cord Blood to Someone Who Needs It?

Donating your baby's cord blood to a public bank is encouraged whenever possible. A list of banks that accept donations of cord blood can be found on the National Marrow Donor Program Web site at www.marrow.org under *Donor Information* or phone 800-627-7692. Not all hospitals collect cord blood, and not all cord blood units can be accepted for storage because of the health history of the parents, the volume of the cord blood collected, or other considerations.

Is the Procedure Used to Collect Cord Blood Safe for My Baby?

Yes. The cord blood is collected after the baby has been delivered and poses no risk to the newborn child or mother. However, there may be some situations when it is not advisable to collect cord blood, such as if you are having twins or your baby is premature. Please check with your doctor before making a decision.

What Does It Cost to Donate or Store Cord Blood?

There is no cost to parents for donating cord blood. Private storage for personal use usually requires an initial fee plus an annual maintenance fee.

Where Can I Get More Information?

You can get more information from the following resources:

- National Marrow Donor Program at 1-800-627-7692 or www.marrow.org
- Blood and Marrow Transplant Information Network at 1-888-597-7654 or www.bmtinfonet.org
- A Parents Guide to Cord Blood Banks http://parentsguidecordblood.org

What can I do with My Baby's Umbilical Cord Blood?

Donate it to someone who needs a transplant …

- Recommended by American Society of Blood & Marrow Transplantation, the American College of Obstetricians and Gynecologists, and the American Academy of Pediatrics.
- Call National Marrow Donor Program at 800-627-7692 or visit www.marrow.org/DONOR/index.html for a list of cord blood banks accepting donations

Store it for private use because the baby's parent or sibling has a disease that can be treated by a cord blood transplant …

- Recommended by American Society of Blood & Marrow Transplantation, the American College of Obstetricians and Gynecologists, and the American Academy of Pediatrics.
- Call Children's Hospital Oakland Sibling Donor Cord Blood Program (CHORI) at 510-450-7600 or the National Marrow Donor Program (see above) for more information

Store it for private use in the future, in case a need arises …

- NOT recommended by American Society of Blood & Marrow Transplantation, the American College of Obstetricians and Gynecologists, and the American Academy of Pediatrics.
- Contact a private cord blood bank. A list of private banks can be found online at http://parentsguidecordblood.org