

REVIEW

Hematopoietic Cell Transplantation With Autologous Cord Blood in Patients With Severe Aplastic Anemia: An Opportunity to Revisit the Controversy Regarding Cord Blood Banking for Private Use

Joseph Rosenthal, MD,^{1,2*} Ann E. Woolfrey, MD,^{3,4} Anna Pawlowska, MD,^{1,2} Sandra H. Thomas, PhD,² Frederick Appelbaum, MD,³ and Stephen Forman, MD²

The controversy surrounding private banking of umbilical cord blood units (CBU), as a safeguard against future malignancy or other life-threatening conditions, raises many questions in pediatric clinical practice. Recent favorable experiences with autologous transplantation for severe aplastic anemia using privately stored CBU, suggested a possible utility. While private banking is difficult to justify statistically or empirically, there may exist rare cases where

autologous transplant of stored umbilical CBU could be beneficial. The reality of privately banked CBU and the possibility for future discovery of additional indications for autologous cord blood transplant, motivated us to re-examine our attitudes towards private cord blood banking. *Pediatr Blood Cancer* 2011;56:1009–1012.
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INTRODUCTION

Hematopoietic stem cell transplantation (HCT) is a potentially curative treatment modality in a variety of genetic, hematologic, and oncologic disorders. Bone marrow or mobilized peripheral blood hematopoietic stem cells (HSC) from allogeneic or autologous sources has been successfully used in the treatment of life-threatening conditions. Human umbilical cord blood contains relatively large numbers of HSC that can be used in life-saving HCT [1]. Since the first report of a successful transplantation in a patient with Fanconi anemia using an umbilical cord unit (CBU) in 1989 [2], there has been a steady increase in the use of CBU as a source for hematopoietic stem cells [3] for HCT. There are now over 120 cord blood banks worldwide; over 900,000 CBUs are stored by the private sector and over 400,000 in public cord blood banks [4]. At present, the use of CBU has been limited, almost exclusively to allogeneic HCT in the treatment of hematological, genetic, and immune deficiency disorders in patients who do not have a matched family or unrelated donor. In comparison, of 14,000 allogeneic HCT from CBU only 100 were done for autologous indications [4].

In the past 3 years we have seen three patients at our respective institutions with severe aplastic anemia (SAA) whose CBUs had been collected at birth and stored for years prior to onset of pancytopenia. At the request of the parents and with the understanding of other options and consent to the experimental nature of the treatment, the patients were treated with an immunosuppressive therapy (IST) followed by HCT from their autologous CBUs. All patients had a complete initial response to therapy and two of the three continue to be disease free for 37 and 58 months, respectively. The third patient experienced SAA recurrence 17 months post-transplant. In the third patient further IST resulted in a partial response and the patient remains transfusion independent for more than 2 years. Although our experience is not sufficient evidence of the validity of autologous cord blood transplant in treatment of SAA, it does provide an opportunity to revisit the issues regarding private collection and cryo-preservation of CBUs for potential use in hematopoietic cell transplantation.

Autologous HCT is not a practical treatment choice in SAA due to primary marrow failure. In fact, only one case has been

reported of successful recovery of hematopoiesis after autologous HCT, and in this case the HSC were collected between aplastic crises [5]. Allogeneic HCT from unrelated CBU transplants has resulted in good outcomes in children and may be associated with reduced risks of graft-versus-host disease compared to HSC obtained from adult marrow or peripheral blood stem cells [6,7]. The moral, social, and ethical perspectives of private banking have been discussed in various forms and reviewed by experts from diverse medical fields [8–11]. There are few recognized indications for autologous HCT in pediatrics and they are primarily for solid tumors such as neuroblastoma, Ewing's family of tumors, and brain tumors. Only a handful of reports have documented the actual use of autologous CBU in HCT for classical hematopoietic disorders, such as ALL and SAA [12,13].

THE CORD BLOOD BANKING CONTROVERSY

Cells obtained from CBU are multi-potent, theoretically capable of restoring hematopoietic, epithelial, endothelial and neural tissues both in vitro and in vivo. Stem cells from CBU are candidates for future use in the treatment of a wide variety of diseases including cardiovascular, ophthalmic, orthopedic, neurological, and endocrine diseases. At this time, however, clinical uses remain in the realm of early exploratory investigation [14]. There is broad consensus that CBUs, a product otherwise discarded, may offer a reliable source of HSC that can be stored, tissue-typed, and made available at short notice [15]. Collecting CBUs on a large scale has potential for improving access to HCT for ethnic groups currently under-represented in the National

¹Department of Pediatrics, City of Hope, Duarte, California;

²Department of Hematology/HCT, City of Hope, Duarte, California;

³The Fred Hutchinson Cancer Research Center, Seattle, Washington;

⁴Seattle Children's Hospital and Regional Medical Center, Seattle, Washington

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*Correspondence to: Joseph Rosenthal, MD, City of Hope, 1500 E. Duarte Rd., Duarte, CA 91010. E-mail: jrosenthal@coh.org

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Marrow Donor Program (NMDP) or other large unrelated donor registries. The merit of public cord blood banking programs such as NMDP, in which parents altruistically donate CBU for potential HCT in unrelated recipients, has long been recognized [15]. Allogeneic HCT from unrelated CBU transplants have outcomes in children similar to those seen with adult marrow or peripheral blood stem cells [6,7,16]. Similarly, double-cord transplants in adults have recently been reported to have outcomes comparable to those seen with matched unrelated donors. In addition to public banking, it is now a common practice to store CBU from newborns in families having a sibling with a known malignant or non-malignant condition that may benefit from HCT. The question under discussion here is whether there is, as the outcome in our three patients may suggest, a benefit to families to store autologous CBU [17–19]?

Clinical Considerations

The primary appeal for parents to collect and store autologous CBU, is the perception of biological insurance [20] as a potential HSC source for future use, should the child develop a condition that constitutes an indication for autologous HCT. The indications for autologous HCT in the pediatric populations are limited to the occasional patient with a recurrent lymphoma and a few selected solid tumors, mostly neuroblastoma. The European Group for Blood and Marrow Transplantation (EBMT) reported that only 650 of a total of 12,732 (5%) autologous HCT were done for pediatric indications in 2000 [21]. This represents less than 1 autologous HCT per million children. The probability for use of an autologous CBU might be slightly higher if one includes SAA, with an estimated incidence of around 3/million in children. Private banks advertise potential use of cord blood for children with leukemia; however, the use of autologous CBU for ALL or AML, the most common indications for HCT in pediatrics, cannot be included in these calculations as autografting is considered inferior to allografting, due to the importance of the graft-versus-leukemia (GVL) effect. Including contributions from all likely autologous CBU uses in pediatrics, translates to a probability of roughly 4/million, or 0.4/100,000, that an autologous, stored CBU could be used to provide a source for an individual HCT. It should be mentioned that for all of these indications, with the exception of aplastic anemia, there are no data to suggest that an autologous cord would have any advantage over autologous cells collected in the conventional manner.

What about the potential for other uses of privately stored CBU? Over the last few years several reports have demonstrated the role of double cord transplants in adults [17,22–24]. This rapidly developing area may result in an increased use for HCT from related, at least partially matched CBUs for family members in need of HCT. Furthermore, as the research in the field of regenerative medicine continues to advance, CBU are increasingly used as cell sources for both cellular or tissue therapies, particularly with respect to multi-lineage differentiation, cord-derived mesenchymal cells, and very small embryonic-like (VSEL) stem cells [23–27]. Hypothetically, there may come a time, when stored autologous CBU becomes an available source for HCT as well as for targeted regenerative therapies; however, this promise is futuristic and, at this time, lacks clinically compelling evidence to justify storage of autologous CBU for possible use in adulthood.

Economic Considerations

Realistically, there appears to be a low probability of needing an autologous transplant from a CBU. The various estimates range from a likely overstated 1 in 10,000, to a more realistic 1 in 250,000 [28]. The price tag for the first year of private storage, including collection, shipping and storage fees, varies between \$1995 and \$2195, followed by an annual storage fee of \$125. More than 210,000 and 145,000 CBU, respectively, were collected by the two largest privately owned cord blood banks in the United States. Of 68 CBU released for transplant from the first bank, 43 were used for allogeneic HCT (hematological malignancies, $n = 30$ and non-malignant disorders, $n = 13$) and 25 were released for use in autologous HCT. The indication for autologous HCT using CBU was SAA in four instances; the other 21 were used for early exploratory investigational indications such as cerebral palsy, diabetes mellitus type I, and anoxic brain injury [29]. Thirty-four of 39 CBUs released from the second bank were for allogeneic HCT; indications for allogeneic HCT included malignancies ($n = 9$) and non-malignant conditions ($n = 25$). Five units were released for autologous HCT for SAA (1), neuroblastoma (1), and brain tumor (1) and 2 CBU were released for early exploratory indications (diabetes mellitus type I and dysgenesis of corpus callosum) [30]. Thus, of more than 355,000 CBU stored in these large 2 banks, 77 CBUs were used for established indications for allogeneic HCT (about 1/4610, or 0.06%) but only 7 units ($<1/50,000$, or 0.0002%) were actually released for autologous HCT, the primary stated goal of these banks. In comparison, the international NETCORD had 6,251 CBU releases of an inventory of 114,546 units (5.4%) for allogeneic HCT done for standard indications [31].

Ethical Considerations

The ethical objections to private collection of autologous CBU include the argument that private CBU banks exploit expectant parents at a time of emotional vulnerability. As expressed by the American Academy of Pediatrics (AAP) Study Group, “Families may be vulnerable to emotional marketing at the time of birth of a child and may look to their physicians for advice. No accurate estimates exist of the likelihood of children to need their own stored cells.” The AAP policy concluded that private CBU banking should not be recommended as biological insurance except for instances where a related family member has a current or potential need for stem cell transplantation. Furthermore, private autologous CBU enterprises may create unequal access due to social and economic gaps in affordability, while public CBU banking aims to increase the pool of available hematopoietic cell sources in ethnic and social groups that are under-represented in the NMDP. Similarly, in 2001 the United Kingdom’s Royal College of Obstetricians and Gynaecologists stated that routine, directed commercial CBU storage could not be justified scientifically, was logistically difficult, and therefore could not be recommended [32]. The French National Consultative Ethics Committee for Health and Life Sciences in 2002 [33] and the European Group of Ethics in Science and New Technologies affiliated with the European Union also reached similar conclusions in 2004 [34]. In addition, in 1999, concern about donor health was raised by the AAP, which suggested that early cord clamping could deprive the infant of a placental blood

transfusion, resulting in lower blood volume and increased risk for anemia later in life [8].

Logistic Considerations

The argument in favor of private collection of autologous CBU is the freedom of choice. If parents make an informed decision, they should have the option of donating cord blood to a public bank or storing in a private bank for autologous or sibling use. Part of the problem is that public banking is not available to many families, depending upon the affiliations of their hospital with public banks. Theoretically, a donation to a public bank could be utilized by the donor (as a perfect match) and could serve both an altruistic and a biological insurance purpose. This public bank option is available only to a small proportion of families, depending on whether their child is delivered at a participating hospital, and even if available, there are quotas for all but under-represented ethnicities.

CONCLUSIONS

When pediatric hematologists/oncologists are asked, as we frequently are, regarding private storage of a newborn CBU, we owe the public an objective, evidence-based answer. At this time, the estimated risk of developing SAA or any of the few indications for autologous HCT in childhood appears to be too low (<1/50,000) to justify the burden on individual families, on medical grounds. However, the lengths to which parents will go to protect their children, from a true or perceived threat, often supersede necessity, and many families would like the option of preserving their child's cord blood. For many families private banking could be a rational, albeit expensive option as a safeguard against future malignancies or for future development in the sciences of cell therapeutics.

From a medical point of view, until further research proves otherwise, directed and private collection and storage of CBU should be encouraged only in cases where a potential use is justified by evidence-based clinical judgment. From a societal perspective, since the inventory of privately stored CBU exceeds that of the public banks, it would make sense to find a way to utilize adequate CBUs from privately stored inventories for well established indications for HCT, when alternative sources are not available. Term duration of storage, *a priori* consents by the donating parents with possible reimbursement for costs, or similar arrangements, might bridge the gap between the principle of freedom of choice and the practical and economic aspects of private banking of CBU.

REFERENCES

1. Broxmeyer HE, Douglas GW, Hangoc G, et al. Human umbilical cord blood as a potential source of transplantable hematopoietic stem/progenitor cells. *Proc Natl Acad Sci USA* 1989;86:3828–3832.
2. Gluckman E, Broxmeyer HA, Auerbach AD, et al. Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical-cord blood from an HLA-identical sibling. *N Engl J Med* 1989;321:1174–1178.
3. Wagner JE, Broxmeyer HE, Byrd RL, et al. Transplantation of umbilical cord blood after myeloablative therapy: Analysis of engraftment. *Blood* 1992;79:1874–1881.
4. Ballen K. Challenges in umbilical cord blood stem cell banking for stem cell reviews and reports. *Stem Cell Rev* 2010;6:8–14.
5. Koza V, Jindra P, Svojgrova M, et al. Successful autologous transplantation in a patient with severe aplastic anemia (SAA). *Bone Marrow Transplant* 1998;21:957–959.
6. Eapen M, Rubinstein P, Zhang MJ, et al. Comparable long-term survival after unrelated and HLA-matched sibling donor hematopoietic stem cell transplantations for acute leukemia in children younger than 18 months. *J Clin Oncol* 2006;24:145–151.
7. Gluckman E, Rocha V. History of the clinical use of umbilical cord blood hematopoietic cells. *Cytotherapy* 2005;7:219–227.
8. American Academy of Pediatrics. Work Group on Cord Blood Banking. Cord blood banking for potential future transplantation: Subject review. *Pediatrics* 1999;104:116–118.
9. Moise KJ, Jr. Umbilical cord stem cells. *Obstet Gynecol* 2005;106:1393–1407.
10. Perlow JH. The case against private umbilical cord blood banking. *Obstet Gynecol* 2005;106:865–866.
11. Steinbrook R. The cord-blood-bank controversies. *N Engl J Med* 2004;351:2255–2257.
12. Hayani A, Lampeter E, Viswanatha D, et al. First report of autologous cord blood transplantation in the treatment of a child with leukemia. *Pediatrics* 2007;119:e296–e300.
13. Fruchtman SM, Hurler A, Dracker R, et al. The successful treatment of severe aplastic anemia with autologous cord blood transplantation. *Biol Blood Marrow Transplant* 2004;10:741–742.
14. Harris DT. Non-haematological uses of cord blood stem cells. *Br J Haematol* 2009;147:177–184.
15. Fisk NM, Roberts IA, Markwald R, et al. Can routine commercial cord blood banking be scientifically and ethically justified? *PLoS Med* 2005;2:e44.
16. Wagner JE, Rosenthal J, Sweetman R, et al. Successful transplantation of HLA-matched and HLA-mismatched umbilical cord blood from unrelated donors: Analysis of engraftment and acute graft-versus-host disease. *Blood* 1996;88:795–802.
17. Jaroscak J, Goltry K, Smith A, et al. Augmentation of umbilical cord blood (UCB) transplantation with ex vivo-expanded UCB cells: Results of a phase I trial using the AastromReplicell System. *Blood* 2003;101:5061–5067.
18. Shpall EJ, Quinones R, Giller R, et al. Transplantation of ex vivo expanded cord blood. *Biol Blood Marrow Transplant* 2002;8:368–376.
19. Robinson SN, Ng J, Niu T, et al. Superior ex vivo cord blood expansion following co-culture with bone marrow-derived mesenchymal stem cells. *Bone Marrow Transplant* 2006;37:359–366.
20. Thornley I, Eapen M, Sung L, et al. Private cord blood banking: Experiences and views of pediatric hematopoietic cell transplantation physicians. *Pediatrics* 2009;123:1011–1017.
21. Gratwohl A, Baldomero H, Horisberger B, et al. Current trends in hematopoietic stem cell transplantation in Europe. *Blood* 2002;100:2374–2386.
22. Barker JN, Weisdorf DJ, Defor TE, et al. Transplantation of 2 partially HLA-matched umbilical cord blood units to enhance engraftment in adults with hematologic malignancy. *Blood* 2005;105:1343–1347.
23. Wang HS, Hung SC, Peng ST, et al. Mesenchymal stem cells in the Wharton's jelly of the human umbilical cord. *Stem Cells* 2004;22:1330–1337.
24. Halasa M, Baskiewicz-Masiuk M, Dabkowska E, et al. An efficient two-step method to purify very small embryonic-like (VSEL) stem cells from umbilical cord blood (UCB). *Folia Histochem Cytobiol* 2008;46:239–243.
25. Lewis ID, Verfaillie CM. Multi-lineage expansion potential of primitive hematopoietic progenitors: Superiority of umbilical

- cord blood compared to mobilized peripheral blood. *Exp Hematol* 2000;28:1087–1095.
26. Goodwin HS, Bicknese AR, Chien SN, et al. Multilineage differentiation activity by cells isolated from umbilical cord blood: Expression of bone, fat, and neural markers. *Biol Blood Marrow Transplant* 2001;7:581–588.
 27. Ortiz-Gonzalez XR, Keene CD, Verfaillie CM, et al. Neural induction of adult bone marrow and umbilical cord stem cells. *Curr Neurovasc Res* 2004;1:207–213.
 28. Johnson FL. Placental blood transplantation and autologous banking—caveat emptor. *J Pediatr Hematol Oncol* 1997;19:183–186.
 29. Cord Blood Registry Stem Cell Therapy Data. http://cordblood.net/pdf/transplant_summary.pdf, 2008.
 30. Viacord. Viacord Proven History of Safe and Effective Units for Transplant. <http://www.viacord.com/2c4e85c5-a0c2-41c4-904a-30ae51f4a118/Link.pdf>, 2008.
 31. Netcord. Netcord inventory and usage March 2008. <https://www.netcord.org/inventory.html>, 2008.
 32. Royal College of Obstetricians and Gynaecologists Scientific Advisory Committee. Umbilical cord blood banking. Opinion paper 2. <http://www.rcog.org.uk/index.asp?PageID=97&PressReleaseID=116>, 2001.
 33. French National Consultative Ethics Committee for Health and Life Sciences. Umbilical cord blood banks for autologous use or for research. Opinion number 74. <http://www.ccne-ethique.fr/english/start.htm>, 2002.
 34. European Group on Ethics in Science and New Technologies. Ethical aspects of umbilical cord blood banking. Opinion of the European Group on Ethics in Science and New Technologies to the European Commission. Available. http://europa.eu.int/comm/european_group_ethics/docs/avis19_en.pdf, 2004.