Cord stem-cell transplantation in Ontario: do we need a public bank?

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ABSTRACT

It has been 21 years since the first successful use of umbilical cord blood as a source of donor cells for hematopoietic stem cell transplantation (HSCT). Over those years, cord blood transplantation (CBT) has shown marked success as an effective modality in the treatment of children and adults with hematologic malignancies, marrow failure, immunodeficiency, hemoglobinopathy, and inherited metabolic diseases. Furthermore, transplantation without full human leukocyte antigen (HLA) matching is possible and, despite a lower incidence of graft-versus-host disease, graft-versus-leukemia effect is preserved. More than 20,000 CBTs have been performed worldwide. Ontario is the most populated province in Canada, and its CBT numbers have increased dramatically in recent years, but most of the umbilical cord blood units are purchased from unrelated international registries. There is no public cord bank in Ontario, but there is a private cord banking option, and notably, Ontario has the largest number of live births in Canada (approximately 40% of all Canadian live births per year occur in Ontario [Statistics Canada, 2007]). In this brief review, the pros and cons of private and public cord banking and the feasibility of starting an Ontario public cord bank are discussed.

KEY WORDS

Cord stem-cell transplantation, public cord banking, private cord banking, children, Ontario

1. INTRODUCTION

In 1989, Gluckman et al.1 published an account of the first successful hematopoietic stem-cell transplantation (HSCT), which used a sibling cord for a child with Fanconi anemia. That procedure was followed by 2 successful transplantations in children that used partially mismatched, unseparated, unrelated umbilical cord blood banked through the Placental Blood Project at the New York Blood Center2.

Since then, thousands of cord blood transplantations (CBTs) have been performed, with very promising results. For example, Barker et al. compared the “gold standard” source of stem cells (bone marrow stem cells) with CBT in children and proved that, although CBT could take longer to engraft and although the incidence of graft failure was higher than that with cells from bone marrow, the outcomes ultimately were similar—mainly because of less graft-versus-host disease (GVHD) and related complications, accompanied by a preserved graft-versus-leukemia effect3. Similar results were reported when 98 adults who received CBT were compared with 584 who received bone marrow stem cells4.

Currently, more than 20,000 CBTs have been reported worldwide, and more than 400,000 cord blood units have been stored in more than 100 cord blood banks5. Umbilical cord blood has emerged in recent years as an attractive alternative to bone marrow stem cells6. Following the international lead, utilization of umbilical cord blood for transplantation has increased in Ontario, in particular for children, because it is much easier to find a suitable cord with enough stem cells (total nucleated cells: >2.5×10^7 per kilogram of recipient body weight) for a child than for an adult. There is, however, no option for public cord donation in Ontario, and cord banking is possible through the private sector only.

2. ADVANTAGES AND DISADVANTAGES OF CBT

The main advantages of cord blood as an alternative source of stem cells are the relative ease of procurement; the absence of risks for mothers and donors; the reduced likelihood of infections, particularly cytomegalovirus, being transmitted; and the almost immediate availability of units that have been fully tested and human leucocyte antigen (HLA)—typed before being frozen. The reduced incidence of GVHD
with preserved graft-versus-leukemia effect is an important benefit for all cords. Furthermore, the ability to use a unit that is partially mismatched is very important for a multi-ethnic population such as Ontario’s, because finding a fully matched unrelated donor for some individuals can be challenging. In seeking living unrelated donors, a full match is required, defined as a 10/10 match on HLA A, B, C, DRB1, and DQB1; however, when seeking a cord, mismatches appear to be better tolerated, with less GvHD. Cords can be 4/6, 5/6, or 6/6 matched for HLA A, B, and DRB1, making it more likely that a cord unit rather than a living unrelated donor can be found for a person from an ethnic minority. Lastly, from a donor perspective, all registered bone marrow donors are adults who need physical assessment, general anesthesia and operating time, and a few days off work for the donation process.

The disadvantages of CBT are mainly a limitation of the cell dose and an increased risk of engraftment failure or delay, with resultant pressure on the length of hospital stay and financial burden. The morbidity and mortality resulting from engraftment failure, delayed engraftment, and delayed immune recovery, with resultant prolonged viral reactivations, are approximately equal to the morbidity and mortality resulting from increased GvHD and related toxicities when cells come from unrelated donors.

2.1 Private Banking

The Society of Obstetricians and Gynaecologists of Canada produced a detailed paper on cord blood banking, in support of altruistic donation, but against private banking for autologous use. Other documents from the United Kingdom by the Royal College of Obstetricians and Gynaecologists and from the United States by the American College of Pediatricians included references to the odds against a child requiring an autologous transplant as being between 1 in 1000 and 1 in 200,000. Private cord banking for autologous transplantation is therefore not encouraged. However, the main potential use for a privately banked cord is an allogeneic graft for a sibling who suffers from leukemia or any condition that is cured by HSCT. Having a banked cord may be life-saving if the donor is so small or so young as to make it difficult to efficiently harvest stem cells—when, for example, the HSCT for the sibling is urgently needed and the matched brother or sister is a neonate or an infant a few weeks old. Furthermore, by allowing for the use of partially mismatched cords, a cord banked from a sibling that is only a 4/6 match would be usable even when bone marrow cells from that sibling would not. For example, data from Eurocord, an international registry that operates on behalf of the European Group for Blood and Marrow Transplantation and that includes both European and non-European centers (1988 to October 2008), indicate that 4875 CBTs have been reported from 233 European transplant centers and 197 transplant centers from other countries. A total of 502 grafts using related donors have been reported (most being HLA-identical sibling donors), mainly for children with malignant and non-malignant disorders. These cords were banked privately for family use and were not publicly available.

Non-hematopoietic stem cells derived from cords also have an important potential use, now and in the future, for regenerative medicine. In 1989, Broxmeyer and colleagues from Indiana University in Indianapolis, United States, systematically analyzed the number of hematopoietic cell progenitors in cord blood for the purpose of using the cells for hematopoietic reconstitution in humans. At that time, the potential for those cells was not known, and some hematologists and transplant physicians regarded this new source of stem cells as “science fiction.” Although the use of such cells in regenerative medicine—which refers to the various research programs aimed at treating disease through the use of non-hematopoietic stem cells (in particular, mesenchymal stem cells), not necessarily through tissue replacement, but through repair of tissues—remains speculative, widely ranging research efforts are underway worldwide. Potential therapies include orthopedic applications such as spinal fusion and cartilage repair, cardiac applications such as treatments for myocardial infarction, and other applications such as amelioration of diabetes and diseases of central nervous system. The benefits of these cord-derived cells are suggested to possibly be superior to those of adult mobilized stem cells, but the benefits can’t accrue to an individual unless the cord blood and early mesenchymal stem cells have been preserved at birth. Currently, it is known that cord stem cells frozen for 15–20 years still have good viability and engraftment potential; whether that situation remains true for 40 or 50 years is unknown. In addition, the repair activity of cord stem cells is still theoretical; these applications cannot be considered to be proven, and only about one third of cord blood units may support enough growth of mesenchymal stem cells. A specific feature of umbilical cord blood mesenchymal stem cells is their low count per volume of initial material and their low proliferative activity.

2.2 Public Banking

Given the increasing demand for unrelated CBT for children and adults who would otherwise have no suitable donors, the donation of cords to a public bank is the ideal option, especially when parents are not considering banking their child’s cord in a private bank. National and international agencies and transplant centers are aware of the need for international standards, the major objectives of which are to promote quality throughout all phases of cord blood...
banking, with the objective of achieving consistent production of good-quality umbilical cord blood units for transplantation. Those standards include collection of cord blood cells; screening, testing, and eligibility determination for maternal and infant donors; processing and storage of units; search registry and search process for the selection of cord units; and transportation and shipping procedures. Practical aspects of cord blood banking such as mother’s consent, collection techniques, labelling and identification, infectious and genetic disease testing, HLA typing, methodology of cell processing, cryopreservation, transportation, and release have been published.

3. THE BIG DEBATE

3.1 Private or Public Banking?

This article has highlighted some important aspects of cord blood stem cell transplantation and emphasized the recent increase in demand for this potentially life-saving procedure. Hence, cord banking and CBT have increased dramatically in recent years. However, for a family who can afford to bank their child’s cord privately and (depending on where they live) also have a public cord banking option, the debate continues: private or public banking?

In 2007, the American Academy of Pediatrics published a policy statement to guide physicians consulting with prospective parents about cord blood banking. They recommended providing the following information:

- Cord blood donation should be discouraged when cord blood stored in a bank is to be directed for later personal or family use, because most conditions that might be helped by cord blood stem cells already exist in the infant’s cord blood (that is, premalignant changes in stem cells). Physicians should be aware of the unsubstantiated claims of private cord blood banks made to future parents that promise to insure infants or family members against serious illnesses in the future by use of the stem cells contained in cord blood. Although not standard of care, directed cord blood banking should be encouraged when a full sibling in the family is known to have a medical condition (malignant or genetic) that could potentially benefit from cord blood transplantation.
- Cord blood donation should be encouraged when the cord blood is stored in a bank for public use. Parents should recognize that genetic testing (for example, for chromosomal abnormalities) and infectious disease testing is performed on the cord blood and that if abnormalities are identified, the parents will be notified. Parents should also be informed that the cord blood banked in a public program may not be accessible for future private use.
- Because no current scientific data support autologous cord blood banking, and because making an accurate estimate of the need for autologous transplantation is difficult and allogeneic transplantation is readily available, the private storage of cord blood as “biological insurance” should be discouraged. Cord blood banks should comply with national accreditation standards developed by the Foundation for the Accreditation of Cellular Therapy, the U.S. Food and Drug Administration, the U.S. Federal Trade Commission, and similar state agencies. At a minimum, physicians involved in the procurement of cord blood should be aware of cord blood collection, processing, and storage procedures.

Notably, the foregoing policy did not comment on the future therapeutic potential of autologous banked cord cells in regenerative medicine, and as it stands today, knowledge about the other potential benefits of these cells is incomplete—in regard, for example, to the potential use of autologous HSCT to ameliorate the course of type 1 diabetes mellitus. Families with strong history of diabetes mellitus may therefore benefit from private cord banking for their children.

When a family asks about cord banking, it is important to explain the facts so that they can then make the decision to bank or not to bank their child’s cord based on family history of certain diseases. Further, the family has to take into account the financial component that is involved in private banking. However, it is every physician’s duty to encourage public cord donation whenever possible.

3.2 Do We Need a Public Cord Bank in Ontario?

As already discussed, some controversies surround private cord banking, and yet it may be crucial for some families with a genetic disease or an unusual cancer gene to bank the cords of their healthy children that might be used in future for an ill sibling. The likelihood of using the stored cord in an autologous transplantation is much less. For other families without a significant history, private banking may not be indicated. However, the choice remains the family’s to make, taking into account their financial status.

On the other hand, donating a cord to a public bank is always indicated. Such donations will help to increase cord availability—in particular, for members of ethnic minorities, given the greater difficulty of finding living unrelated donors for them. One of the main advantages of the umbilical cord blood approach is the potential to target, in a noninvasive manner, ethnic groups that are underrepresented in the adult unrelated donor pool. But, there first has to be a public cord bank to donate to. Ontario, the most populous province in Canada, currently has no option for public cord banking, and cords not banked privately are wasted. (Naturally, not all cords
It is estimated that more than 400,000 cord blood units in more than 100 cord blood banks in many countries are available for transplantation, and Ontario transplant centers have access to many of these international cords. However, having a local public cord bank would certainly be a bonus for Ontario residents because the likelihood is much higher of finding cord donors from a local public bank than from foreign international cord banks. Furthermore, money spent to purchase foreign cords would be well spent supporting the establishment of an Ontario public cord bank. That being said, the process of establishing a cord bank—infrastructure, personnel, equipment, and all the necessary accreditation—is a prolonged and costly process. Ontario would therefore be better served by establishing a mini public cord bank within an already established facility.

One example of such a facility is the Canadian Blood Services blood and stem cell laboratory, where space, personnel, and accreditations are already in place. Some expansion in resources would be necessary to accommodate this envisioned mini public cord bank, which could potentially serve Ontario and other Canadian provinces as a national bank. Such a bank could quickly start to accept donated cords from children born in Ontario, building up an inventory of cord units that are frozen and ready to be released—initially within Ontario, and then, as cord numbers grow, possibly to other provinces and to international recipients. By situating a public cord bank in Ontario, more control and uniformity are likely to be achieved in the donor questionnaire and in the testing, processing, and measuring of cell counts and viability. Moreover, given the multi-ethnic nature of Ontario residents, including families with rare haplotypes and children of mixed marriages, donations from those populations to a public bank would make cords available to other children from similar ethnic and mixed-marriage backgrounds.

6. CONFLICT OF INTEREST DISCLOSURES

The author has no conflicts of interest to declare and is not affiliated with any private or public cord bank in Canada or elsewhere.

7. REFERENCES


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