Blood Reviews 25 (2011) 255–259

Contents lists available at SciVerse ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/blre

REVIEW

Milestones in umbilical cord blood transplantation

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ARTICLE INFO

Keywords:
Umbilical cord blood
Allogeneic transplants
Mismatched donors
Blood banks
History
Graft versus host disease
Transplant-related mortality

ABSTRACT

Since the first human cord blood transplant, performed in 1988, cord blood banks have been established worldwide for collection and cryopreservation of cord blood for allogeneic hematopoietic stem cell transplant. Umbilical cord blood (UCB) has now become one of the most commonly used source of hematopoietic stem cells for allogeneic transplantation. Today a global network of cord blood banks and transplant centers has been established for a common inventory with an estimated 600,000 UCB have been banked and more than 20,000 UCB units distributed worldwide for adults and children with severe hematological diseases. Several studies have shown that the number of cells is the most important factor for engraftment while some degree of HLA mismatches is acceptable. The absence of ethical concern, and the unlimited supply of cells explain the increasing interest of using cord blood for developing regenerative medicine.

1. Introduction

Since the first human cord blood transplant, performed in 1988, cord blood banks have been established worldwide for collection and cryopreservation of cord blood for allogeneic hematopoietic stem cell transplant.[1] These advantages were first recognized in CBT using related donors; secondarily, cord blood banks (CBB) established criteria for standardization of cord blood collection, banking, processing, and cryopreservation for unrelated donor transplants in patients with various hematological malignant and non malignant diseases.[2] Umbilical cord blood (UCB) has now become one of the most commonly used source of hematopoietic stem cells for allogeneic transplantation. Today a global network of cord blood banks (CBB) and transplant centers has been established for a common inventory, an estimated 600,000 UCB have been banked and more than 20,000 UCB units distributed worldwide for adults and children with severe hematological diseases. Several studies have shown that the number of cells is the most important factor for engraftment while some degree of HLA mismatches is acceptable. The absence of ethical concern and the unlimited supply of cells explain the increasing interest of using cord blood for developing regenerative medicine.

2. Pre clinical steps

The concept of using cord blood was developed in the late 1970s, however the pivotal work of H.E. Broxmeyer moved UCB from the laboratory to clinical practice. H.E. Boyse provided the proof of concept studies in mice while H.E. Broxmeyer systematically evaluated the hematopoietic potential of human UCB in vitro and developed practical and efficient methods for large volume collection and storage of UCB. It was postulated at that time that UCB collected at birth might contain enough hematopoietic stem/progenitor cells for clinical use.[3] This possibility was strengthened by the knowledge that hematopoietic progenitor cells from UCB could be maintained for many weeks in long-term cultures suggesting their production from more primitive cells. Mice studies showed that small amounts of neonatal blood but not small amounts of adult blood allowed survival of approximately half of the lethally irradiated mice. This led to a multi institutional study that addressed the following: 1) estimation of the reconstituting cellular content of cord blood by measurement of hematopoietic progenitor cells numbers and comparison with adult bone marrow 2) collection, 3) transportation and 4) optimal cryopreservation of cord blood. They found on 101 samples, collected in New York and analyzed in Indiana University School of Medicine, that the number of progenitors was in the lower range of numbers associated with successful engraftment and, that the numbers were improved if there was no attempt of erythrocyte removal.[4] They noted that samples could be successfully frozen, stored and thawed without major loss. At that time, it was felt, by this group, that cord blood stem cells would be especially attractive for autologous purpose making available for a recipient a perfectly matched set of stored cells in the future. However, it was unlikely that autologous cord blood transplantation would be tested in the near future. This concept led to a long-lasting debate on patenting cord blood for clinical use and of setting up commercial cord blood banks for personal use. Testing the concept of allogeneic cord blood stem cell transplants, in which an HLA identical sibling was available, was discussed. The first umbilical cord blood transplant (UCBT) was made possible by an intensive collaboration between three groups: A.D. Auerbach from the Rockefeller University in New-York (USA) described a method of prenatal diagnosis in Fanconi anemia (FA),[5] H.E. Broxmeyer from Indiana University in

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doi:10.1016/j.blre.2011.06.003

Indianapolis (USA) systematically analyzed the number of hematopoietic cell progenitors in cord blood for the purpose of using the cells for hematopoietic reconstitution in humans and E. Gluckman, from Hospital Saint Louis in Paris (France) showed that the in-vivo hypersensitivity of FA cells translated in an increased toxicity of the pre transplant conditioning regimen used in aplastic anemia and, she was the first to use a modified attenuated dose conditioning in these patients with improved short and long term survival.[6]

A.D. Auerbach selected mothers of FA patients who were pregnant; she made a prenatal diagnosis on cultured amniotic fluid cells and she was able to select 5 mothers who were expecting a baby who was known, before birth, to be unaffected with FA and HLA identical to the patient. Based on the preceding information, umbilical cord blood was harvested and cryopreserved at birth. It was felt by all involved and the human subjects institutional review boards of the involved centers that the availability of cord blood in this case obviated the need for bone marrow aspiration from the infant sibling although the infant sibling was available for bone marrow donation if necessary.

3. From the first umbilical cord blood transplant to the development of umbilical cord blood banks

The first UCBT was performed in 1988 in a patient with FA.[1] This patient had a healthy HLA identical sibling shown by prenatal testing to be unaffected by the disorder, to have a normal karyotype and to be HLA identical to the patient. Her cord blood was collected at birth, cryopreserved and used after thawing for transplantation. The patient was conditioned by a procedure developed specifically for the treatment of FA patients who are extremely sensitive to the administration of alkylating agents like Cyclophosphamide. This patient was conditioned with a low dose of Cyclophosphamide (20 mg/kg instead of 200 mg/kg) and 5 Gy total lymphoid irradiation. The frozen cells were hand-delivered from Indiana to Paris in a dry shipper that maintained the temperature at −175°C. The cells were thawed without further processing on day 0. Thawed cells were tested for viability and progenitor assays and results were similar to the counts recorded before freezing. First signs of engraftment appeared on day 22 with subsequent complete hematological reconstitution and donor chimerism. The patient had no GVHD and is currently healthy more than 20 years after UCBT, with a complete long-term hematological and immunological donor reconstitution.

This first success opened the way to a new field in the domain of allogeneic hematopoietic stem cell transplant (HSCT) as it showed that: 1) a single umbilical cord blood contained enough hematopoietic stem cells to reconstitute definitely the host lympho-hematopoietic compartment; 2) an umbilical cord blood unit could be collected at birth without any harm to the new-born infant, and 3) umbilical cord blood hematopoietic stem cells could be cryopreserved and transplanted in a myelo-ablated host after thawing without losing their repopulating capacity. Since, our knowledge on the biological characteristics of umbilical cord blood cells has increased, emphasizing the advantages of using umbilical cord blood stem cells for transplant.[7–13]

Several aspects were identified as subject of further questioning and investigations: Would a single cord blood unit contain enough stem cells to permanently engraft children and adults? Would maternal cell contamination in fetal blood engraft and give severe GVHD? Would the same results be obtained in patients transplanted for other indications than Fanconi anemia such as leukemia? Would they engraft also in adults? Are the properties of hematopoietic cord blood cells different from adult cells? What are the immunological properties of cord blood cells? How does it interfere with graft versus host disease, graft versus leukemia and immune reconstitution? Is the immune immaturity of cord blood lymphocytes able to overcome the HLA barrier and authorize HLA mismatched transplants? Is it possible to establish cord blood banks for unrelated and related transplants? What would be the criteria for collection, quality control and cryopreservation? Would it be possible to collect cord blood not only for familial transplant but also for unrelated transplants? What would be the size of this bank if it was demonstrated that HLA incompatibilities would not be recognized because of the immaturity of the immune system at birth? All these questions have been answered during the last 20 years thanks to the worldwide development of intense international cooperation, in Europe with Eurocord and Netcord, in the USA with CIBMTR and NMDP, with Asia cord, Australia Cord and single transplant centers.

4. Milestones in the development of CBT

- Optimization of UCB collection and storage.[2,3,14]
- First HLA identical sibling cord blood transplant in a patient with Fanconi anemia.[1]
- Development of CBB for related and unrelated transplants (Paris, Dusseldorf, New York, Milan).[15]
- First unrelated mismatched cord blood transplant in children.[16]
- First unrelated cord blood transplant in adult.[17]
- Creation of the Eurocord Netcord network.[18]
- Description of criteria of donor choice based on number of cells and possibility to use mismatched cord blood.[19,20]
- Demonstration that in HLA identical sibling transplants cord blood gave delayed engraftment, less GVH and same survival.[21]
- Demonstration that compared to matched unrelated bone marrow, mismatched cord blood gave similar long term leukemia free survival in children[22,23,28] and in adults.[24–27]
- Improvement of results mostly in adults by double cord blood transplants and non myelo-ablative conditioning regimens.[35,36]
- Isolation of non hematopoietic stem cells from cord blood as a first step for regenerative medicine.[38]

5. International organization of cord blood transplant

Since the first UCBT, more than 20,000 CBT have been reported worldwide and more than 600,000 cord blood units have been stored in more than 100 cord blood banks (www.bmdw.org) (www.nmdp.org).

The main practical advantages of using cord blood as an alternative source of stem cells are the relative ease of procurement, the absence of risk for mothers and donors, the reduced likelihood of transmitting infections, particularly CMV, and the ability to store fully tested and HLA typed transplants in the frozen state, available for immediate use.

Eurocord was established in 1995, its principal objectives were to collect outcomes data provided by cord blood banks and transplant centers. Eurocord has collected, from 1988 to October 2010, 6736 UCBT from European transplant centers and transplant centers from other countries. Five hundred and ninety six transplants have been reported using related donors (majority of HLA identical sibling donors), mainly for children with malignant and non malignant disorders and, 6140 have been performed in the unrelated transplant setting for children (n = 3287) and adults (n = 2770). In order to promote education and information, Eurocord has launched a new European program entitled: an On-line CME program in cord blood technology and transplantation for providing a learning tool on the scientific, technical, clinical, regulatory aspects of cord blood, easily accessible at a time and language convenient for users www.eurocord-ed.org. Based on this international cooperation Eurocord has published crucial reports which have been the basis of the rapid development of cord blood transplant.

`Netcord was created in 1998 to establish good practices in umbilical cord blood storage, facilitate donor search, improve the quality of the grafts, standardize excellence criteria on an international scale and importantly establish procedures for bank accreditation. The inventory of Netcord, the cooperative network of large experienced UCB banks, currently has more than 300,000 cryopreserved UCB units ready for clinical use for unrelated recipients and more than 8624 grafts shipped.