

Cord blood banking and accreditation

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Cord blood banking is a sequential process including a number of steps starting from donor informed consent and donor selection, followed by collection of maternal and paternal medical history, cord blood collection, unit transportation from the delivery room to the bank, cord blood unit processing, characterization and cryopreservation, unit release for transplantation, and ending with the evaluation of clinical outcome.

Cord blood banking requires a carefully designed quality system. Of the different models available, we based the initial development of our quality system on the ISO 9000 standard. After ISO 9000 certification, we started the process of accreditation by the Foundation for the Accreditation of Cellular Therapy (FACT), which was obtained in 2004. The accreditation process includes submission of documentation in English to demonstrate compliance with the *NetCord/FACT International Standards for Cord Blood Collection, Processing, Testing, Selection and Release*, now available in its third edition, which is followed by an on-site inspection. Other organizations such as the AABB and the National Marrow Donor Program have developed other cord blood banking accreditation and cooperative programmes.

Based on the expectation of a more widespread clinical use of cord blood, efforts should be developed to harmonize national and international cord blood banking accreditation schemes.

Keywords: blood banking, stem cells, regenerative medicine.

Introduction

Cord blood (also known as placental blood) is the newborn's blood remaining in the placenta after delivery. Its regular collection and banking, which was started in the early 1990s, was prompted by the observation that cord blood contains a number of haemopoietic progenitor and stem cells capable of repopulating a myeloablated human recipient. The main current clinical use of cord blood is allogeneic transplantation in patients suffering from severe blood diseases such as leukaemia, lymphoma, haemoglobinopathies and congenital immuno-deficiencies [1–3]. At present, more than 250 000 cord blood units are stored in 39 large allogeneic banking

programmes for family related and unrelated recipients, located in 21 Countries (source: BMDW website). Approximately one half of the allogeneic worldwide inventory is managed by the NetCord foundation [4], which has recently agreed to share cord blood unit searches with the National Marrow Donor Program (NMDP). The 18 NetCord cord blood banks have distributed 2824 and 2079 cord blood units that have been transplanted in children and adults, respectively (source: NetCord website, NetCord inventory and use October 2006).

The aim of this article is to describe the core elements of cord blood banking and to review the current status of cord blood banking accreditation.

Cord blood banking

Cord blood banking can be divided into a number of sequential steps [5]: (i) delivery of information to the mother and collection of the informed consent; (ii) collection of maternal and paternal medical history; (iii) cord blood collection; (iv)

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Table 1 Objectives of the Milano Cord Blood Bank

1. To provide a service of cord blood collection and cryopreservation for allogeneic unrelated and related clinical transplantation.
2. To ensure safety and efficacy of cord blood units through the adoption of a quality system.
3. To implement cooperation at the national level (Italian network GRACE, Italian Group for Bone Marrow Transplant – GITMO) and at the international level (NetCord, EUROCORD, EBMT).
4. To monitor the clinical outcome of cord blood transplants performed with units released by the Milano Cord Blood Bank.
5. To develop studies on cord blood biological characteristics and cord blood processing for banking purposes.

collection of maternal samples; (v) samples and unit labelling and transportation to the bank; (vi) unit preliminary evaluation (volume and cell count determinations), testing, processing, cryopreservation, quality control; (vii) storage of the unit and the associated samples; (viii) unit human leucocyte antigen (HLA) typing, haemopoietic colony and CD34+ cell count; (ix) data recording; (x) unit validation; (xi) data sharing with cord blood registries; and (xii) management of compatible unit requests.

Besides the standard mandatory minimum requirements, the development of each bank's specific standard operative procedures (SOP) depends on the bank's objectives. As an example, Table 1 reports the objectives of the Milano Cord Blood Bank (MICB), which started its activity in 1993. After a pilot programme, the bank became fully operative in 1996 [6]. MICB has been managing the cord blood registry of the Italian banks affiliated in the GRACE (Gruppo per la Raccolta e Amplificazione delle Cellule Emopoietiche – Group for the Collection and Expansion of Hemopoietic Cells) network during 1997–2007. Since 1 February 2007, the task of managing the cord blood registry has been given to the Italian Bone Marrow Donor Registry in Genova, Italy [7].

The next few paragraphs describe the main elements of cord blood banking at the MICB.

Standard operation time at the MICB is from 8 : 00 to 20 : 00 h, Monday to Friday. Allogeneic unrelated cord blood collections are not performed at times (e.g. weekends, holidays) that do not allow completion of unit's cryopreservation within 36 h from collection. Collections for related recipients are performed at any time and managed by on-call staff. In addition to the procedures related to cord blood banking, the MICB staff provide cryopreservation and storage of bone marrow and peripheral blood stem cells for autologous and allogeneic transplant.

The MICB facility includes an area of 226 m², split into 172 m² of the cryobiology area and 54 m² of the processing laboratory and administrative office. Access to the bank and to the cryobiology area is regulated according to different levels of authorization. The cryobiology area is fully compliant with safety regulations and equipped with acoustic and visual alarms. Moreover, automated video recording is activated when operators enter the area. Digital images are stored for 10 years.

A disaster/emergency plan has been developed to ensure staff and products safety. Priority to unit transfer into an alternative cryogenic area has been given to related cord blood units and to any other haemopoietic progenitor units collected for autologous transplant or for a specific patient.

Cord blood collections are performed in 20 delivery rooms at hospitals located within a maximum distance of 300 km from the MICB. The midwife staff of each delivery room are trained according to a specific programme. The activity of each collection site is audited yearly.

Gynaecologists and midwives select potential cord blood donors at predelivery courses, mostly during the regular clinical evaluations carried out before delivery, or at the predelivery hospital admission.

The exclusion criteria are as follows:

1. Lack of consent
2. Risky behaviours in the mother and/or the father:
 - Use of heavy drugs
 - Sex with risky behaviour partners
3. Positive serology of the mother and/or the father for:
 - Hepatitis: HBsAg, anti-hepatitis C virus (HCV), HCV-RNA.
 - AIDS: anti-HIV.
 - Syphilis: Treponema Pallidum Hemagglutination Assay (TPHA) or Venereal Disease Research Laboratory (VDRL).
 - Anti-human T-cell lymphotropic virus (HTLV) I–II.
4. Genetic diseases in the mother, father and/or baby.
5. Stay for more than 6 months in the UK during 1980–96.
6. Obstetrical exclusion criteria:
 - Delivery before 34 weeks of gestation
 - Congenital abnormalities in the newborn
 - Body temperature in the mother >38 °C during 24 h before and after delivery
 - Fetal distress

A detailed list of conditions that prevent cord blood collection is enclosed in the SOPs available at the bank and at the collection centres.

Cord blood is collected in a plastic bag from the placenta *in situ* in physiological deliveries and after placental delivery in Caesarean sections. A maternal venous blood sample is collected for serological screening and HLA typing.

The units are transported to the MICB under controlled temperature conditions. Temperature is monitored with an electronic device located in the container used for transportation.

Besides temperature, transportation recorded parameters include the times of packaging, start and end of transportation and the name of the operator. The units and the maternal samples are discarded if cord blood was collected more than 36 h before, the medical history form discloses exclusion criteria, the bag is damaged, and the unit or the maternal samples are mislabelled.

Moreover, the units with net cord blood volume (i.e. without anticoagulant) below 60 ml and the units with volume greater than 60 ml and number of total nucleated cells (NC) below 1000×10^6 are discarded, used for research or quality control. The units with volume greater than 60 ml and NC count equal to or greater than 1000×10^6 undergo volume reduction after centrifugation with a bottom-and-top procedure operated with the automated blood component fractionator Compomat G-4 (Fresenius, Germany). The procedure collects a buffy-coat fraction of 39 ml. After volume reduction, the unit is rejected if the total NC count is below 800×10^6 . Finally, the units are cryopreserved v/v with 80% dextran +20% DMSO (10% final concentration) with a validated automated controlled-rate freezing device [8].

The routine unit quality control of volume reduction includes NC percent recovery on all processed units and percent recovery of CD34 + cells and of colony forming units (CFU) on 5 random units each month.

Critical quality control procedures are carried out at four process phases: (i) at banking, (ii) on samples collected 6 months after delivery, (iii) when a transplant centre requests further investigations, and (iv) before unit release.

In summary, the cord blood banking process carried out at the MICB includes the elements/steps described below.

(1) Informed consent form signed by the mother. The informed consent form is available and stored for both banked and non-banked units.

(2) Clinical history of the mother, the father and their families.

(3) Unit's volume evaluation and NC count before and after volume reduction.

(4) Nucleated red cells count.

(5) ABO and Rh blood groups.

(6) HLA-A, B and DRB1 (high resolution) typing on both unit and mother samples, carried out with genomic technics by the European Federation for Immunogenetics (EFI)-accredited laboratory of our Department. Upon request, other HLA loci can be typed and the unit contamination with maternal DNA can be evaluated by microsatellite analysis.

(7) Evaluation of CFU-granulocyte macrophage (GM), CFU-granulocyte-erythrocyte-macrophage-megakaryocyte (GEMM), burst forming units-erythrocyte (BFU-E) and CD34 + cell count.

(8) Abnormal haemoglobin screening.

(9) Search for aerobic and anaerobic bacteria and antibiogram if the test is positive. The test is performed on the final product, after adding the freezing solution.

(10) Serological screening carried out on maternal serum collected at delivery: HBsAg, anti-HIV 1-2, anti-HCV, HCV/HIV-RNA, HBV-DNA, TPHA, ALT, anti-HTLV I-II, antiHbc, anti-cytomegalovirus (CMV) and anti-toxoplasma (IgG and IgM).

(11) Serological screening on a unit sample for HBsAg, anti-HIV 1-2, anti-HCV, and anti-HTLV I-II.

(12) CMV-DNA evaluation, when IgM anti-CMV is positive; this test is performed on a thawed sample from a frozen bag segment.

(13) Mother and baby check 6 months after delivery. A maternal blood sample is collected. The mother is interviewed to check her medical history form collected at delivery and to collect the postnatal baby's medical history. A certificate issued by the baby's paediatrician is collected. The current 6-month return rate of the mothers is 94% [9]. If the mother is not available for the 6-month check, this information is released to the clinician at the time of unit request.

(14) Serological screening on fresh maternal serum collected 6 months after delivery. The screening includes: HBsAg, anti-HIV 1-2, anti-HCV, TPHA, alanine aminotransferase (ALT), anti-HTLV I-II, anti-CMV and anti-toxoplasma (IgG and IgM).

(15) Maintenance of a frozen repository of biological samples from all units and mothers.

(16) Data sharing with national and international registries. The data (unit code, HLA type and NC count) are sent to registries after encryption with a public and a private key by using the PGP software.

(17) Quality control before unit release on a thawed sample from a segment cryopreserved and stored under the same physical conditions as the bag, including: (i) cell viability; (ii) nucleated cell count; (iii) clonogenic potential; (iv) search for aerobic and anaerobic bacteria and antibiogram if the test is positive; (v) HLA-A, B, DRB1 confirmatory typing; and (vi) HLA-A, B, DRB1 low resolution typing on a maternal sample collected at the 6 months check, or if the sample is not available, on a sample collected at delivery (frozen buffy-coat).

(18) Unit validation before release for transplantation. The validation procedure requires that all assay results are within predefined acceptable ranges and comply with signed original laboratory reports.

(19) Unit transportation to the transplant centre with a dry shipper at -150°C .

(20) Regular monitoring of clinical outcome data. Reports are received from the clinical data monitoring unit of Eurocord located in Paris.

Accreditation of cord blood banks

Cord blood banking requires a carefully designed quality system. Of the different models available, we based the initial development of our quality system on the ISO 9000 standard [10,11]. After the ISO 9000 certification of our facility, we

started the process of accreditation by the Foundation for the Accreditation of Cellular Therapy (FACT), which was obtained in 2004. As reported at the FACT website, 12 cord blood banks have been accredited so far. They are located in Arcadia, USA (StemCyte); Barcelona, Spain; Besancon, France; Edgware, UK (London Cord Blood Bank); Durham, USA (Carolinas Cord Blood Bank at Duke); Düsseldorf, Germany (José Carreras Cord Blood Bank Düsseldorf); Helsinki, Finland; Houston, USA (MD Anderson Cord Blood Bank); Liège, Belgium; Milan, Italy; New York, USA (National Cord Blood Program); and Pavia, Italy.

The FACT accreditation process includes submission of documentation in English to demonstrate compliance with the *NetCord/FACT International Standards for Cord Blood Collection, Processing, Testing, Selection and Release*, now available in its third edition, which is followed by an on-site inspection based on a check list including almost 400 check points. The accreditation fee structure includes a non-refundable registration fee of \$US5000 and a cord blood bank initial inspection fee of \$US15 000. The latter covers the inspection of the bank, of the processing facility and up to 15 collection sites. The outcomes of the inspection are recorded in a report which is reviewed together with the checklist by the Accreditation Coordinator and approved by the FACT Medical Director. An inspection summary is then submitted to the Cord Blood Accreditation Committee, which determines the accreditation outcome. The accreditation period is 3 years. Additional information is available at the FACT website.

The AABB accreditation programme is described at the AABB website, which includes a useful FAQ document on umbilical cord blood donation. This document is intended to assist with educating the public. According to the AABB programme, accreditation implies that 'an AABB assessor has been on the facility's premises and the facility practices were found to conform with the AABB standards of practice' [12]. In a table updated on 12 January 2007, the AABB listed 24 accredited cord blood banks in the USA, six in Taiwan, five in Canada, and one each in Japan, Korea, Israel and Singapore. More detailed information on the AABB accreditation programme can be downloaded from the AABB website Members Area.

The NMDP presents in its website the Center for Cord Blood, through which 'the NMDP establishes relationships with cord blood banks throughout the United States as well as international cord blood banks' [13]. They also list 23 cord blood banking facilities within the USA that participate in their programme. A document (number A00092 version 2-0, June 2006) that can be downloaded from the website describes the NMDP Cord Blood Bank Participation Criteria. Additional information relevant for cord blood banks is contained in the nineteenth edition of the NMDP Standards.

Besides accreditation processes and multi-institutional cooperation programmes, another important action for cord

blood banks interested in releasing their products into the USA is registration with the Food and Drug Administration (FDA). In fact, the regulatory framework for human cells, tissues and cellular and tissue-based products (HCT/P), which includes cord blood and was fully implemented in May 2005, 'requires that establishments register with FDA and list their products, ensure quality control by adhering to the agency's current good tissue practices and follow the agency's rules on donor eligibility. Under this framework, cord blood hematopoietic stem/progenitor cells from unrelated donors are regulated as both HCT/P and as biologic drugs subject to licensure' [14]. Moreover, units collected on or after 25 May 2005, must comply with a 'donor eligibility rule' that defines the 'requirements to screen and test donors of human cell, tissue, and cellular and tissue-based products (HCT/Ps) for risk factors for, and clinical evidence of, relevant communicable disease agents or diseases' [15].

Conclusions

The pioneering phase of cord blood transplantation is rapidly evolving into an established procedure for bone marrow replacement suitable for both paediatric and adult recipients, although improvements are needed in particular for the latter category of patients. In this regard, studies on double-cord transplant, reduced intensity conditioning regimens and alternative administration routes have already yielded encouraging results [16,17]. Efforts from the cord blood banking community to enlarge the worldwide allogeneic altruistic inventory, as recommended by the Institute of Medicine [18], with preferential banking of large volume units, can contribute to the optimization of the clinical results.

The above scenario suggests that urgent actions are needed to harmonize the requirements of national and international cord blood banking accreditation programmes, because of: (i) the frequent need to ship compatible units across national borders; (ii) the expected increase of cord blood therapeutic use [3]; (iii) the long-term investments required in several countries to increase the current inventory [19]; and (iv) the expansion, despite the lack of scientific evidence [20–25], of autologous cord blood banking.

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