

Umbilical Cord Blood: Medical Waste or Important Source of Stem Cells?

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Abstract

The identification of new sources of stem cells may provide significant clinical benefits in the regenerative medicine. Although sometimes still regarded as a medical waste, the blood remained in the umbilical vein after birth (Umbilical Cord Blood, UCB) has become a valuable alternative source of haematopoietic stem cells for the treatment of various disorders.

Using UCB is advantageous because it is obtained by a simple, safe and painless procedure when the baby is delivered. The immaturity of UCB cells resulted in a reduced graft-versus-host disease when compared to bone marrow grafts. Furthermore, there may be particular utility in using UCB in the context of HLA mismatch between available donor and recipient. However, due to the limited number of stem cells, the progress in the field has been largely restricted to children. Nevertheless, evidence supporting the efficacy of a double transplant of UCB in adults has significantly increased over the past years, as an alternative to bone marrow transplantation in those adult patients where no compatible donors are available.

Today, new parents may choose to have the UCB stored in a stem cell bank. These banks can be public (non-profit) or private (for-profit). The public banks store UCB from donors and provide it when transplantation is prescribed to an unrelated patient. Unfortunately, donation to a public bank is not possible everywhere, although their number is growing. On contrary, the private banks offer a commercial service to parents in order to preserve the UCB for future needs of their child. Storing UCB in such private banks is controversial and recommended only in the case of historical existence of a genetic disease; otherwise the likelihood of stored UCB being used in autologous transplant is negligible. This and other ethical aspects of UCB banking are discussed in this paper.

Keywords: Stem cells; Umbilical cord blood; Transplantation; Banking; Private bank; Public bank

Introduction

Stem cells are ideal candidates for the regenerative medicine, tissue engineering and cell replacement therapy, mainly due to their ability to differentiate into multiple cell lines [1]. Basic research on embryonic stem cells has contributed to our knowledge about the developmental potential and plasticity of stem cells. Unfortunately, they can also form tumors and are ethically controversial due to their origin in human embryos [2]. Increasing evidence indicates that stem cells can also be isolated from adult and immature tissues, such as bone marrow, adipose tissue, cord blood, or placenta, which are generally indicated as adult stem cell sources [3]. These cells represent a valuable alternative to the more controversial embryonic stem cells.

Adult stem cell transplantation has been proved an effective therapy for many serious diseases, malignant and non-malignant. Depending on circumstances, the cells can be harvested from the patient (autologous transplantation) or from a donor (allogenic transplantation). Currently, the main sources of hematopoietic stem cells used in transplantation are bone marrow (BM), peripheral blood (PB), and umbilical cord blood (UCB). After transplantation, these hematopoietic stem cells can repopulate the bone marrow of the patient, providing a source of blood cells [3].

The use of UCB as source of stem cells is a relatively new field. Among the pioneers in this field is Hal E. Broxmeyer. He started in 1974 from the observation that UCB contained a large number of granulocyte and macrophage forming cells [4]. His subsequent experiments have shown that blood collected from newborn mice contained progenitor cells capable of reconstituting the bone marrow into lethally irradiated mice [5]. These valuable observations have led to the first studies on human material. Thus, it was demonstrated that human UCB obtained from normal or premature deliveries contained a sufficient number of stem and progenitor cells to support the transplantation with durable engraftment [6]. Not only the number of hematopoietic progenitors was higher, but their proliferative capacity was 20 times higher in UCB compared to PB. In culture, CD34⁺ cells (stem/progenitor cells) isolated from UCB proliferated much faster than similar cultures from BM and in addition, generated a greater number of progenitors [7]. These pre-clinical data constituted the starting point of the first clinical studies with UCB that have resulted in the emergence of UCB banks.

Aspects Related to UCB Transplant

UCB represents the blood remained in placenta and attached umbilical cord after delivery. It is collected at delivery time, after detaching the umbilical cord from the neonate. Its collection does not damage the newborn, because it occurs post-natal from an organ that is not useful anymore either for baby or for mother, and that otherwise would be discarded together with the placenta. Once collected, the blood

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Received March 12, 2012; Accepted March 30, 2012; Published April 05, 2012

Citation: Burlacu A (2012) Umbilical Cord Blood: Medical Waste or Important Source of Stem Cells? Human Genet Embryol S2:005. doi:10.4172/2161-0436. S2-005

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is tested, frozen and stored in banks for future use in transplantation therapy. It is called cord blood unit.

The research point of view regarding the abundance of UCB in hematopoietic stem cells tempted the general reconsideration of the status of UCB in 1992 from biological waste to an important source of stem cells [8]. The potential advantages of using UCB versus other sources of adult stem/ progenitor cells include: the immediate availability, the low-cost and facility of harvesting, low risk of donation (the collection of UCB occurs subsequent to baby delivery, therefore there is no risk either for newborn or mother), the high percentage of stem/progenitor cells able for long-term repopulation, increased capacity of proliferation, minimal manipulation before infusion, low risk of transmitting infections and developing graft versus host disease [9].

The availability of UCB is immediate owing to the fact that the processing for cryopreservation occurs simultaneously with the analysis of sample (cell content, disease status and HLA typing). This makes the cells available at whatever time a unit has been identified as being suited for a patient [9]. In contrast, when BM transplantation is to be performed, the donor is first contacted and the cells are subsequently donated with a considerable delay from the decision of transplant. It is often happens that the BM donor is not available anymore by the time a transplant is decided, either due to the change of address, the medical status in that moment, or simply the demur to donate [9].

In some cases, such as those of high risk acute leukemia or immunodeficiency, these delays are a major problem. Therefore, the average length of time required to identify an unrelated BM donor extended around 49 days, with variation between 32 and 393 days, whereas the period needed to identify a UCB donor is usually 13.5 days, with variations between 2 and 387 days [10]. Moreover, it is attempted that spreading out the UCB banks would still reduce the period needed for finding a suitable donor up to one single day [11]. This would be a real important progress especially for patients with rapid progressing disorders. Accordingly, the physicians would have the option of using UCB whenever a rapid intervention is needed. Unfortunately, the clinical importance of this advantage is not yet known, because nearly all publications have first excluded the possibility of finding a BM donor before considering UCB for transplantation [10]. This shows that UCB is considered only as the second option of stem cell source, being offered mainly to high-risk patients.

The immunoreactivity of the effector cells in UCB (i.e., monocytes and lymphocytes) seems to be lower compared to that of adult peripheral blood [10]. This low immunoreactivity can be attributed to the immaturity of the lymphocytes, which was also suggested by numerous studies. Thus, phenotypic comparisons between PB and UCB have shown that although the number of B cells was similar, about half of the B cell population in UCB had an immature phenotype. Furthermore, T cell population in UCB also contains an increased number of naïve cells [10]. The decline in T cell number resulted in a decreased release of certain mediators during activation, and thus an ineffective cell response to mitogen stimulation and a lower risk of developing graft- versus-host disease (GVHD) after transplantation. GVHD, in mild or severe forms, is the common complication after allogenic transplantation, representing the leading cause of death. Anyway, the frequency of this disease is lower after transplantation of cord blood units and furthermore, in the case the disease is generated, its form is much easier compared to that developed after other forms of transplantation [12].

Another consequence of the immaturity of the lymphocytes in UCB is the common tolerance and therefore the matching is less important in UCB transplantation than in the case of PB transplantation, although the higher match the better. In adult stem cells transplantation, the degree of match between the donor and recipient is very important for the successful of the transplantation and any HLA mismatch is considered a high risk [9]. Therefore, for a patient having a less frequent tissue type, the doctor may consider UCB transplant as an option, even if a similar donor is not found. UCB properties lead to less stringent criteria of compatibility between donor and recipient that increase the potential number of units available for a patient; consequently, there is an increased probability in finding a donor, with no risk of developing GVHD [13].

Although clinical results are encouraging, the use of UCB in transplantation has several disadvantages: (i) an insufficient total number of stem/progenitor cells that limits their use only in children patients; (ii) delays in the immune and hematopoietic reconstitution as a consequence of UCB immaturity; (iii) risk of disease returning due to the weak graft-versus-host reaction; (iv) increased risk of transmission of genetic diseases, due to the impossibility to track the donor growth and development [9].

As the success of the transplantation (providing hematopoietic recovery) obviously depends on the number of infused cells, the main disadvantage of using UCB for transplantation remains the limited number of stem cells which can be collected from one placenta, in average 10° cells. There is a threshold effect in the amount of cells needed in allogenic transplant, in terms of early and sustained grafting: low dose of stem cells are often associated with partial and delayed engraftment and consequently partial and delayed immune reconstitution [10].

Establishing the minimum number of cells must take into consideration the cell grafting, the incidence of post-transplant events and the rate of neutrophil and platelet recovery and accordingly, the recipients of higher doses of cells have faster recovery. The minimal dose of stem cells for a successful transplantation was empirically established as being 1.7 x 105 CD34+cells/ kg body weight or 2.5 x 107 mononuclear cells per kg body weight [6]. Unfortunately, the number of cells in UCB is limited by the amount that can be harvested from a placenta, so that the recipient body weight restricts the choice of UCB as the stem cell source for transplantation. In addition, while the quantity required for transplantation of PB cells can de expanded by removing cells several times from the same donor at selected intervals, such additional stem cell infusions are impossible in the case of UCB transplantation [10]. For such cases, the doctors may only choose for a second unit, which unavoidably is different from the first one, to accomplish a second transplant to the same patient, in the case the cells were not engrafted during the first procedure [14]. Due to the limited number of stem/progenitor cells contained in one cord blood unit, UCB transplant is made more frequently in children, while adult patients require larger amounts of cells. Nevertheless, this therapy is becoming applicable even in adults provided that two blood units are used [15]. In such procedures, the units are administered either sequentially (within 30 min) or within 6 hours apart, after confirming

that the first unit has been successfully infused [16]. In the majority of patients undergoing double UCB transplant, a transient chimerism, which is due to the presence of cells from both donor units, is noticed early post transplant; however, three weeks after transplantation, in more than 85% of patients the long-term hematopoiesis is sustained by only one of the infused cord blood units, which become dominant [17]. According to Eurocord Registry data, double UCB transplantation has been applied in around 1000 adult patients with hematological diseases and this number has even surpassed the number of adults transplanted with single cord blood units [18]. Furthermore, an improved engraftment has been reported in adults having double cord blood unit transplantation, which partially overcame the influence of up to two HLA disparities [19].

Another potential strategy for UCB transplant therapy to become applicable in adults is to increase the number of cells within one unit by culturing the cells in the laboratory, before being transplanted into an adult patient. Although this idea is attractive, the first studies asserted there were no significant improvements in the success rate of transplant when UCB cells were expanded ex vivo [10]. On the other hand, some improvements have been achieved by introducing stem cells directly into the BM to avoid their partial loss by grafting into other tissues. Being a relatively new option for transplant, this strategy still requires a further period of study. Currently, doctors do not have much information on long-term results of such processes, as they have for other transplants.

Another disadvantage of using UCB in transplantation is given by the delay in hematopoietic and immune reconstitution, as a consequence of the low number of mature lymphocytes. Thus, the grafting period of UCB cells after transplantation (representing the period required for transplanted cells to initiate growing and create other blood cells and a new immune system) is consistently higher than with other cell sources, which increases the risk for infection [12]. The renewal of the neutrophils and platelets is delayed in UCB transplantation, irrespective if the donor is related or not. The average period of neutrophil recovery (representing the time required for the neutrophils to attain the normal concentration into the blood) is 20-30 days in adults (0.5 x 106 neutrophils/ml), while in children is lower, consistent with the smaller number of cells needed to be formed [15]. So far, no differences were reported between the rates of neutrophil recovery in children with transplant from related or unrelated donor. On contrast, comparative studies have shown that patients undergoing transplantation for the treatment of a malignant disease had a high probability of grafting compared to those with a non-malignant disease, even if cell doses and HLA match level were similar [6]. This demonstrated that the initial diagnosis affects the grafting, perhaps reflecting an intact immune system in patients with non-malignant disease, who are more resistant to chemotherapy before transplantation.

Clinical Data

The first transplantation with UCB was done between brothers in 1989 [20]. Since then, UCB has become an increasingly popular alternative to transplantation with PB and BM, particularly in children. Approximately 2000 children with hematological malignancies have been transplanted with related or unrelated cord blood transplantation from 1990 to 2008 [18]. The first report of autologous transplantation with UCB was made in 2007, by a group from Advocate Hope Children's Hospital of Ilinois, USA [21]. The patient was a three-year old girl with leukemia, whose chemotherapy had failed and thus the transplant became the only possibility for saving her. Molecular testing was performed on the cord blood for the detection of the leukemia clone. Fortunately, it was not found, showing that the leukemia was not present at birth. The transplant occurred 10 months after diagnosis while she was receiving chemotherapy. Transplantation had been successful at the time of reporting (4 months post-transplantation), blood composition was normal and the patient was healthy with no serious complications or GVHD.

A study on the effectiveness of sibling HLA-identical stem cell transplantation for hematological malignancies was recently published [22]. In that study, 50 women delivering healthy babies who already had a sibling with disease (acute lymphoblastic leukemia, acute myeloblastic leukemia, non-Hodgkin lymphoma or chronic myeloid leukemia) that was potentially treatable with allogeneic cord blood transplants were considered. Among enrolled families, 4 children needed transplantation and the results were successfully. One of the children (CML) had no available UCB unit, due to damaged cord/placenta at delivery. In that case, as the preimplantation HLA-genotyping had revealed the HLA similarity between siblings, bone marrow cells from the donor at the age of 18 months were transplanted to the affected sibling resulting in successful hematopoietic reconstitution. In other two children, the transplantations were made with UCB units from unrelated donors, due to HLA-mismatched cord blood. Finally, only one received the sibling cord blood unit. The recipient was a 3-year old boy with ALL in second remission and cord blood from his sister had been collected 8 months earlier. Bone marrow cells from the same HLA-matched sibling were used as alternative allogeneic hematopoietic stem cells, because the number of cord blood nucleated cells was considered insufficient to ensure engraftment.

The autologous transplantation with UCB has been also reported in diabetic patients, after in vitro studies had previously shown the ability of stem cells in UCB to generate peptide C or insulin producing cells [23]. Thus, a pilot study published in 2008 demonstrated the effectiveness of autologous infusion of UCB in 15 children with type 1 diabetes by slowing down the loss of endogenous insulin production. Three mechanisms have been advanced as possibly being responsible for reducing the autoimmune processes: (i) stem cells migrate to the damaged pancreas and differentiate into insulin-producing cells; (ii) stem cells induce the formation of new islets by stimulating the proliferation of islets remained in the viable tissue; (iii) T cells in UCB facilitate the suppression of effector T cells and allow the restoration of tolerance through their inhibitory effects on multiple cell types [23].

Despite the difficulties described above, UCB has a growing usage even in adults. Two publications in 2004 in New England Journal of Medicine drew attention to this type of transplantation in adults. One of these studies considered 600 acute leukemia patients who underwent transplantation with hematopoietic stem cells [24]. Of these, 100 patients received UCB and the others received BM. All BM recipients were perfect compatible with the donors, while more than 90% of UCB recipients had differences in at least one HLA antigen from the donor. The results showed a lower incidence of GVHD after transplantation with UCB, even if accompanied by a delay in the hematopoietic recovery. Nevertheless, the recovery rate, the survival and, most important, the mortality associated with transplant were similar in the two groups [24]. The second study compared the effect of transplantation with hematopoietic stem cells from different sources in patients with acute leukemia [25]. One group received BM cells with perfect matched HLA antigens, the second group received BM cells with 5/6 identity in HLA antigens between donor and recipient, while the third group received UCB with one or two differences in HLA antigens. The conclusion at the end of the study was that the hematopoietic recovery was slower in adults who received UCB, which was also predictable considering that they received a smaller number of cells. Also predictably, the patients who received perfect compatible transplantation had the best recovery. However, there were no differences with regard to mortality and morbidity between the three groups [25]. Although the slow or incomplete grafting is still a problem, these studies demonstrate that UCB, even when differed of that of the recipient, is a reasonable alternative source of stem cells for those adults who can not find perfect compatible donors.

A disputed strategy, but leading to the most promising results obtained so far, is the concomitant transplantation of two cord blood units with similar HLA (that is called the double UCB transplantation) with the obvious aim of increasing the dose of transplanted cells in adults or older teenagers. A study reported in 2006 [14] showed that double UCB transplantation in adults had led to a faster recovery of neutrophils (in average, after 23 days) after mieloablative preparative therapy and to a more consistent grafting (90% in average). These results were comparable with results typically seen in pediatric transplantation. Although more studies are still needed to better understand the relative impact of using two cord blood units, this study showed that the technique was feasible and, interestingly, one of the donors became dominant by day 100. These results have led to an increasing interest in using UCB as a source of stem cells in adults.

Stem Cell Banks

In order to have cord blood cells available for transplantation a number of banks were created worldwide. Currently, all new parents may choose to have the UCB stored in a stem cell bank. At present, there are around 100 UCB banks worldwide (around 40 in Europe, 30 in US and Canada, 20 in Asia, 10 in Australia and none in Africa). These banks of umbilical cord blood can be commercial (if the blood is collected from the baby's umbilical cord and stored exclusively for the benefit of that child or his relatives, with the cost being supported by the baby's family) or public/non-profit (the blood is preserved and offered at request to donor-unrelated patients).

The first operational public UCB banks were created in New York, Milan and Düsseldorf [26], allowing unrelated UCB transplantation to become an option for patients lacking a suitable adult donor. The hematology center in New York, led by Dr. Pablo Rubinstein, has initially set up the protocols for collecting, processing and preserving the cord blood units [26]. According to a study in 2009, there are about 400,000 cord blood units available in 35 banks in 21 countries [12]. All these units are characterized for A, B and DR HLA antigens, and are integrated in various programs that facilitate the finding of a compatible donor. These public banks may provide cord blood cells to any person (unrelated patient) who has been prescribed transplantation. Unfortunately, donation to a public bank is not yet possible everywhere, although the number of public banks is growing.

Unlike the public banks that have been gaining more popularity for the last years, private banks are controversial by both the medical

community and civil society [13,27]. Although there is nothing wrong in offering a commercial service to parents in order to preserve the cells to be used for their child in the future, the controversies are related to its collection and storage for the use of only few possible recipients. According to statistics performed in 2008, only 0.001% of the children whose blood has been preserved at birth utilized this stock [28]. It is therefore highly hypothetical that cord blood cells kept for autologous use will be of any value in the future. For this reason, storing UCB in such private banks is recommended only in the case of historical existence of a genetic disease.

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Ethical Aspects of Umbilical Cord Blood Banking

Ideally, parents should have access to a neutral source of information about the utility of UCB and their various options: discarding UCB, storing it in a private bank, or donating it to a public bank. This source should also provide information about the need for research to further develop its potential. Many physicians involved in the care of pregnant women do not provide much information on UCB collection and use, and future parents are sometimes left with documentation from private banks and what information they can find independently as their only sources of information on these topics [29]. There are several ethical and moral concerns related to the documentation provided by the private banks (European group on ethics in science and new technologies, 2004 [29]. One of these concerns refers to the distortion of the reality in order to attract more donors. Thus, commercial providers have often the tendency to quote figures of the probability of needing an autologous transplant at least an order of magnitude higher [27]. Another ethical aspect is the emotional exploitation of future parents in a period of maximum vulnerability. It is obvious that the time of pregnancy and birth represents a period when parents might be very sensitive to any statement regarding their child. In these settings, the commercial providers can easily exploit the emotional vulnerabilities of parents, by saying that banking is a "once in a lifetime opportunity" and "no one has a second chance to collect their cord blood" (http://www. cordbloodbanking.com /tag/umbilical-cord-blood/). Although there is nothing wrong in advising parents to store their child's stem cells, such approach is unethical because it might result in the acceptance of any conditions without a correct judgement. Therefore, European Union guidance recommends the parents to be told that the likelihood of stored UCB stem cells being used to treat their child is negligible.

Final Remarks

What conclusions can be drawn at this time regarding the potential and actual use of UCB? The UCB transplantation from closely related donors with perfect match is already established in children and represents the treatment of choice in a number of genetic diseases, blood malignancies and immune deficiencies, for example leukemia. In adults, the problem of the limited number of stem cells is not yet solved and is translated into a 10-15% risk of cellular grafting failure or important delay in hematopoietic reconstitution. This further means longer period of follow-up care with both economic and clinical consequences. Nevertheless, in the case an adequate dose of stem cells from one single cord blood unit is available, UCB represents a viable alternative. Also, those adults for whom other sources of stem cells are not available can entry into a still experimental program to use two or more cord blood units. Preliminary data have demonstrated the safety of double umbilical cord blood transplantation; however the ongoing clinical trials and prolonged follow up of the patients will clarify the immunology and determine the efficacy of this approach [16].

The importance of using UCB is best illustrated by the circumstance where HLA differences exist between donor and acceptor, in which case UCB transplant gives superior results than any other type of transplant. Acceptance of donors with HLA mismatches increases the complexity and toxicity of the transplantation, which translates into increased morbidity and mortality associated to transplantation. Therefore, the use of these new methods of treatment is still being limited to clinical studies.

Acknowledgements

This work was supported by a grant from the Romanian Ministry of Education and Research, RU-TE88/2010. The author acknowledges the financial support of European Social Fund – "Cristofor I. Simionescu" Postdoctoral Fellowship Programme (ID POSDRU/89/1.5/S/55216), Sectoral Operational Programme Human Resources Development 2007 – 2013.

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This article was originally published in a special issue, **Epigenetics**, **stem cells and tumorigenicity** handled by Editor(s). Dr. Yue Zhang, Harvard Medical School, USA; Yujing Li, Emory University School of Medicine, USA; Yanhong Ji, Xian Jiaotong University, China transplantation. Haematologica 96: 1213-1220.

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