Umbilical cord blood stem cells: clinical trials in non-hematological disorders

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Background: Umbilical cord blood (UCB) has become the second most common source of stem cells for cell therapy. The recent boom in stem cell research and public fascination with promises of stem cell-based therapies, fueled by the media, have led researchers to explore the potential of UCB stem cells in therapy for non-hematological disorders.

Sources of data: ClinicalTrials.gov database searched with key words ‘cord blood stem cells’ on December 28, 2011.

Areas of agreement: As a rich source of the most primitive hematopoietic stem cells, UCB has a strong regenerative potential in stem cell-based-therapy for hematological disorders.

Areas of controversy: Potential of UCB stem cells in therapy for non-hematological disorders.

Growing points: Increasing number of clinical trials with UCB stem cell-based therapy for a variety of diseases.

Areas timely for developing research: A need for standardization of criteria for selection of UCB units for stem cell-based therapy, outcome measures and long-term follow-up.

Keywords: umbilical cord blood stem cells/clinical trials/non-hematological disorders

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Introduction

Bone marrow hematopoietic stem cell (HSC) transplantation is the oldest and the most successful type of stem cell therapy. The first successful cord blood transplant was in 1988 to treat a 5-year-old boy suffering from Fanconi anemia. Since then, umbilical cord blood (UCB) has emerged as an alternative to bone marrow as a rich source of the
most primitive HSC capable of repopulating a recipient \textit{in vivo} with hematopoietic progenitor cells (HPCs), and in 2009, UCB became the second most common source of stem cells for cell therapy. Currently, the global network of cord blood banks has an estimated inventory of 600,000 UCB units, and >20,000 units have been distributed for treatment.\textsuperscript{2} In comparison with other sources of HSC for cell-based therapy, the main advantages of UCB are as follows: (i) procurement is easy and carries no risk for the donor, (ii) fully tested, HLA-typed samples can be cryopreserved and distributed for future use, (iii) there is minimal chance of contamination with cytomegalovirus or Epstein–Barr virus because of low placental transmission rates and (iv) there are minimal ethical concerns associated with the procurement of the samples. Although UCB is primarily a source of HSC and HPC, more recently evidence emerged that UCB contains relatively heterogeneous cell populations including mesenchymal stem cells (MSCs), multipotent adult progenitor cells, unrestricted somatic stem cells, endothelial progenitor cells and immature immune cells.\textsuperscript{3,4} All of them have a regenerative potential, which is, however, limited by the number of the cells that can be obtained through \textit{ex vivo} expansion for the purpose of clinical transplantation.

\textbf{Cord blood banking}

In response to the potential of UCB stem cell-based therapy, a large number of private/commercial and public cord blood banks have been established worldwide. When UCB is donated to public banks, identifying information is removed and samples can be used for anyone in need. In the majority of public banks, the criterion for an UCB unit to be considered for storage is $>10^9$ total nucleated cell count, which can normally be obtained only if the volume of collected UCB is larger than 90 ml (an average is $10^7$ total nucleated cells per ml of collected UCB). Due to an insufficient number of nucleated cells, ca. 60\% of collected UCB is discarded.\textsuperscript{5,6} The minimum threshold for an optimal UCB transplant is $2.5–5.0 \times 10^7$ total nucleated cells/kg of recipient’s body weight and with appropriate human leukocyte antigen (HLA) matching one UCB unit can be sufficient for a donor of \~20–40 kg.\textsuperscript{6}

In private/commercial banks, the parents retain custody of the cryopreserved UCB with the theory that the donor or an HLA-matched relative can use the sample at some point in the foreseeable future. Private/commercial banks charge a fee to cryopreserve the collected UCB (Table 1). Relying on yet unsuccessful expansion technology, they attract often ill-informed customers with promises that everything is/will be possible.\textsuperscript{7,8} The total nucleated cell count for rejecting collected UCB samples is lower than in public banks and units are rarely
discarded. For example, Virgin Health Bank offers the Community Banking service in which the family retains control of the stem cells from the first 5 ml of UCB collected for 25 years, whereas the remaining cells are donated to public banks.

Impact of HLA compatibility on engraftment and survival

The standard for adult unrelated-donor transplantation requires the donor and recipient to be fully matched at HLA-A, -B, -C and -DRB1, with high-resolution typing for all loci, whereas accepted standards for selecting UCB stem cell transplant donor–recipient matches remain lower. Since the first successful partially HLA-matched transplantation of UCB from an unrelated donor, it has gradually become a standard that for HSC from UCB a match is only required at the antigen level for HLA-A and -B and at the allele level for -DRB1. Although multiple studies have evaluated the impact of low-to-intermediate HLA typing resolution and undetected disparity at the outcome of UCB stem cell transplants, the optimum HLA typing criteria for selection of UCB units for stem cell-based therapies remain ambiguous. Even though there might be a correlation between high-resolution HLA typing and favorable outcome, one has to keep in mind two limitations of these studies: (i) majority of UCB stem cell transplants have been 1 or 2 antigen mismatched and only a relatively small proportion of pediatric patients received fully HLA-matched transplants and (ii) patient

Table 1 Costs of UCB cryopreservation and storage.

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<th>Bank</th>
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<td>1852</td>
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</table>

All prices are in US dollars (USD). Conversion rate: 1 GBP = 1.55 USD. To obtain the pricing, the following websites were accessed on January 20, 2012:
CryoCell: www.cryo-cell.com/services/pricing.asp;
Cryo-Save: www.cryo-save.com/uk/cryocord1.html;
Future Health: www.futurehealthbiobank.co.uk/services/cord-blood-cells?v=pricelist;
Virgin – family: www.virginhealthbank.com/our-services/family-banking;

*aPrice is for 21 years of storage.
*bPrice is for 18 years of storage.
*cFamily will only retain the stem cells from the first 5 ml of cord blood collected and all the remaining cells will be donated to the public through the cell donation program.
age and cell dose might be confounding variables. These other factors, such as depletion of erythrocytes prior to cryopreservation or freezing/thawing procedures, which may later influence engraftment or survival.

**Additional selection criteria**

Some studies have suggested that besides HLA matching, the dose of CD34+ cells or the graft progenitor cell content, as measured by colony-forming cells, are relatively important determinants of hematopoietic recovery post-UCB transplant. Since the methodologies for quantification of CD34+ or colony-forming cells are not standardized, the data are likely to vary from bank to bank. The total nucleated cell count is recognized as a critical factor and it remained the most widely accepted standard for selection of UCB units for stem cell transplants.

**Applications in non-hematological disorders**

The recent boom in stem cell research and public fascination with promises of stem cell-based therapies, fueled by the media, have led researchers to explore the potential of UCB stem cells in therapy for non-hematological disorders. To get an overview of clinical trials with UCB stem cells, we searched the ClinicalTrials.gov database with key words ‘cord blood stem cells’ on December 28, 2011. ClinicalTrials.gov is a registry of governmentally and privately supported clinical trials in the USA and worldwide. The database contains over 118,000 trials conducted in all 50 states and in 178 countries and receives >50 million page views per month. Although it is unlikely that all or even the majority of clinical trials with UCB stem cells in the world are registered in this database, the information should reflect the overall picture of what is currently going on in the field.

Our search found 231 studies, 171 of them relevant. Thirty-one studies were for non-hematological disorders (Table 2). The studies explore the effects of UCB stem cell transplantation in 15 different conditions. Inborn metabolic disorders with eight trials and diabetes with four trials top the list. The USA was the leading country in sponsoring trials for both hematological (117) and non-hematological disorders (21), which is not surprising since the database is USA based (Table 3). Besides the USA, 13 countries were sponsoring trials for hematological disorders and only 5 for non-hematological disorders. South Korea was leading as a sponsor for non-hematological
disorders (4). Whereas academic institutions sponsored the majority of trials, 11 companies were sponsoring clinical trials for hematological and two, one in Korea, one in China, for non-hematological

<table>
<thead>
<tr>
<th>Condition</th>
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<tr>
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<td>Critical limb ischemia</td>
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SLE, systemic lupus erythematosus.

*Clinical trials that involve both hematological and non-hematological disorders.

<table>
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*Two clinical trials involve both H and non-H disorders.
disorders. For hematological disorders, the majority of companies were USA based (8).

**Alzheimer disease**

Alzheimer’s disease is neurodegenerative disorder and one of the most prevalent causes of cognitive decline in elderly leading to complete loss of independence. A research group from South Korea published a study in which UCB-derived MSC co-culture reduced the hippocampal apoptosis induced by amyloid-β peptide treatment. Moreover, Alzheimer’s disease in a mouse model treated with UCB-derived MSC demonstrated cognitive rescue with restoration of learning/memory function. Clinical trial NCT01297218 sponsored by South Korean company Medipost (http://eng.medi-post.co.kr) is aimed at evaluating the safety and tolerability of their UCB-derived MSC product NeuroStem®-AD. The beneficial effect of transplanted cells might also result from stimulation of the systemic immune system of donor, which will help to protect or repair brain tissue.

**Autism**

Autism spectrum disorders are characterized by social interaction abnormalities, impaired verbal and non-verbal communication and repetitive, obsessive behavior. Although the etiologies of autistic disorders remain unknown, there is an increasing evidence of autoimmune phenomena in individuals with autism. Antibodies directed against the fetal brain have been detected in some mothers of children with autism and immune system dysfunction may represent novel targets for treatment of autistic disorders. Since human umbilical cord MSC and UCB mononuclear cells have been shown to have the ability to modulate the immune response, Chinese company Beike (http://beikebiotech.com) is evaluating them in the clinical trial NCT01343511 as a novel therapeutic strategy for treatment of autistic disorders.

**Bronchopulmonary dysplasia**

Bronchopulmonary dysplasia is the most common serious pathological condition of premature birth with lung inflammation being a major contributor to the pathogenesis of the disease, which is further exacerbated by mechanical ventilation and exposure to supplemental oxygen. In clinical trial NCT01297205, sponsored by South Korean company Medipost, investigators are evaluating the safety and the tolerability of
Medipost’s UCB-derived MSC product PneumoStem® in premature infants with bronchopulmonary dysplasia. A single dose of 10 or 20 million cells per kg of body weight is administered intratracheally with a hope that the cells will help regenerate the lungs.

Burns

In clinical trial NCT01443689, Chinese company Beike is evaluating the effects of allogeneic umbilical cord MSC and UCB mononuclear cell transplantation in patients with acute, moderate-severe and full-thickness burns.

Cartilage injury and osteoarthritis

In vitro studies suggest that UCB-derived MSC have chondrogenic potential. In order to stimulate the regeneration of defective cartilage tissue and improve function, in the clinical study NCT01041001, sponsored by South Korean company Medipost, UCB-derived MSC product CartiStem® is mixed with a semisolid polymer and administered into the cartilage tissue lesion.

Cerebral palsy

Cerebral palsy is a group of conditions caused by damage to centers in the brain controlling movement of different areas of body. UCB stem cells have been used experimentally in animal brain injury models. Whereas in some studies they appear to have a beneficial effect, the findings are not consistent, and other groups have not seen any effect in similar systems. The clinical trial NCT01072370, conducted in Atlanta, Georgia, is to test the safety and effectiveness of an autologous UCB infusion in children who have motor disability due to cerebral palsy and whose parents have saved their UCB. The clinical trial NCT01193660, conducted in South Korea, is to determine the efficacy of autologous UCB in a combination with erythropoietin.

Critical limb ischemia

Critical limb ischemia is a severe obstruction of the arteries resulting in decreased blood flow to the point of severe pain, skin ulcers and sores. If not treated, the endpoint is often amputation of the affected limb. The clinical study NCT01019681 is to determine whether treatment...
with UCB stem cells will improve blood flow to the most severely affected leg of a participant with medically refractory and non-surgical peripheral vascular disease of the lower extremity. The study followed a report by the same group on the safety and feasibility of autologous CD133\(^+\) cell implantation into the lower extremity muscles of patients with critical limb ischemia in which limb salvage was achieved for seven of the nine treated patients.\(^3^2\)

**Diabetes**

Type 1 diabetes is an autoimmune disease characterized by T-cell-mediated destruction of insulin-producing pancreatic β cells and lifelong dependence on exogenous insulin administration. Given the differentiation propensity of UCB stem cells, it is highly unlikely that type 1 diabetes patients could benefit from traditional UCB stem cell transplant. However, a study in an animal model suggested that UCB stem cells may help patients to regenerate their native population of islet β cells without stem cell transplantation through ‘stem cell education’ of patient’s T-cells\(^3^3\) and this alternative approach has been employed in one of the trials (NCT01350219). UCB stem cells from healthy donors were adhered to disks made of special hydrophobic material and cultured in a specifically designed ‘Stem Cell Educator’ device in serum-free medium for 2–3 weeks until 80–90% confluence was reached.\(^3^4\) Lymphocytes isolated from the blood of type 1 diabetes patients were slowly passed through a nine-layer stack of disks full of allogeneic adherent UCB stem cells. The patient’s lymphocytes were exposed to UCB stem cells for 2–3 h in the device. Such ‘educated’ lymphocytes were then collected and returned to the patient. Pancreatic islet β cell function was assessed by measuring basal and glucose-stimulated C-peptide production over a 24-week period. Although the data demonstrated at some length the feasibility and safety of the approach, it is still debatable whether reversal of autoimmunity using UCB stem cells is realistic as a treatment for type 1 diabetes. The same approach is used in a clinical trial for type 2 diabetes (NCT01415726).

Loss of tolerance, characteristic in diabetes, is largely related to innate defects in the immune system. The patients exhibit a variety of abnormalities in immune function including a deficiency in regulatory T cell subpopulation. In the study NCT00873925, recently diagnosed type 1 diabetics on intensive insulin therapy, who have UCB cryopreserved, undergo a single infusion of autologous UCB followed by 1 year of dietary supplementation of vitamin D and omega 3 fatty acids. The hypothesis is that such a regimen will preserve better pancreatic β
cell function as measured by glucose-stimulated C-peptide production following the 1-year mixed meal tolerance test. Preliminary observations suggested an increase in regulatory T cell population in the peripheral blood >6 months after UCB infusion. Recent results demonstrated that autologous UCB infusion in children with type 1 diabetes is safe and induces changes in regulatory T cell subpopulation frequency but fails to preserve C-peptide.

In the clinical trials NCT00989547, the investigators’ goal is to transfuse autologous UCB stem cells into children with type 1 diabetes in an attempt to regenerate pancreatic β cells and improve blood glucose control.

**Epidermolysis bullosa**

Epidermolysis bullosa is a diverse group of inherited disorders that cause increased skin fragility of which recessive dystrophic epidermolysis bullosa is the most severe. There is currently no single optimal therapy for these patients, but cell therapy holds great potential. The report that in a murine model, wild-type, congenic bone marrow cells homed to damaged skin, produced type VII collagen protein and anchoring fibrils, ameliorated skin fragility and reduced lethality led to the underlying hypothesis of three human clinical trials (NCT01033552; NCT00881556; NCT00478244). The premise is that the infusion of bone marrow or UCB from a healthy unaffected donor will correct the gene deficiency and reduce the skin fragility characteristic of severe forms of epidermolysis bullosa. A secondary hypothesis is that MSC from a healthy donor will enhance the safety and efficacy of the allogeneic HSC transplant as well as serve as a source of renewable cells for the treatment of focal areas of residual blistering. In an initial report, six children with recessive dystrophic epidermolysis bullosa received iminoablative chemotherapy and allogeneic bone marrow stem cell transplantation. The investigators were able to detect the presence of donor cells and collagen VII depositions in all treated patients. However, how and whether HSC from bone marrow and UCB can alter skin architecture and wound healing in a robust, clinically meaningful way is still unclear.

**Hearing loss**

A study by Revoltella et al. provided evidence of positive engraftment of intravenously transplanted human UCB CD133+ cells into the inner ear of NOD-SCID mice rendered deaf with kanamycin and noise. The
clinical trial NCT01343394 is to see if autologous UCB treatment is safe for children with acquired hearing loss, and to determine if the treatment improves the late functional outcome. The recently FDA-approved year long study will follow 10 children, ages 6 weeks to 18 months and to ensure consistency in UCB processing, storage and release for infusion, only one stem cell bank, Cord Blood Registry (www.cordblood.com) will be providing clients for the study.

Inborn metabolic disorders

In the most cases, cross-correction is the idea behind stem cell therapy of inborn metabolic disorders, mostly mucopolysaccharide and lysosomal storage disorders. Engrafted donor leukocytes in the host tissue make and secrete the deficient enzyme, which is then taken up by residual enzyme-deficient host cells. The first HSC transplantation for an inborn metabolic disorder was 20 years ago in the UK, for a patient suffering from Hurler’s syndrome. Hurler’s syndrome is a genetic deficiency of α-L-iduronidase, a lysosomal enzyme that degrades the complex macromolecular glycosaminoglycans of heparan and dermatan sulfate. Although stem cell therapy can ameliorate symptoms, it cannot cure any of these disorders.

Clinical trial NCT01238328 is evaluating the efficacy and side effects of donor HSC using a chemotherapy regimen without total-body irradiation in children undergoing an HSC transplant for mucopolysaccharidoses. The blood stem cells will be derived from either related donor or unrelated UCB or haploidentical donor.

The studies NCT00668564, NCT00383448, NCT00176917 and NCT00176904 are all conducted at the University of Minnesota in Minneapolis with the aim to evaluate the ability to achieve and sustain donor engraftment in patients with a variety of inborn metabolic disorders. The outcome after allogeneic HSC transplantation for childhood cerebral adrenoleukodystrophy (part of NCT00668564 and NCT00176904 trials) has been recently reported.

The study NCT00654433 sponsored by Durham, North Carolina-based Aldagen (www.aldagen.com), was evaluating the effect of the aldehyde dehydrogenase-bright (ALD-101) subpopulation of UCB stem cells as an adjuvant to standard UCB stem cell transplant in a variety of inherited metabolic disorders. The study, however, has been suspended.

Two of the studies, NCT00950846 and NCT00920972, are not limited to inborn metabolic disorders, but also include hematological disorders. The investigators aim to address engraftment, incidence of acute and chronic graft versus host disease, incidence of infections,
immune reconstitution and overall survival in congenital childhood disorders after UCB stem cell transplant. The study NCT00950846 is examining the effect of preconditioning with busulfan, cytoxan and fludarabine on engraftment, whereas the NCT00920972 study is to determine if treatment with alemtuzumab, fludarabine and melphalan followed by related/unrelated bone marrow, peripheral blood stem cell or UCB cell transplant will result in donor engraftment.

**Osteopetrosis**

Autosomal recessive osteopetrosis is a rare, lethal disorder in which osteoclasts are absent or non-functional, resulting in a bone marrow cavity insufficient to support hematopoiesis. Osteoclasts are derived from hematopoietic precursors and there is a hope that allogeneic HSC transplantation can cure the bony manifestations of the disorder. The first studies using HLA-matched bone marrow transplantation done 25 years ago have shown that osteoclasts differentiated from the donor’s marrow were functional and able to ameliorate some of the symptoms.

Clinical studies NCT00775931 and NCT00638820 are exploring whether HSC transplant, either from the bone marrow or UCB, would have a better engraftment in a combination with chemotherapy and radiation. In contrast clinical study NCT01087398 is evaluating the efficacy and side effects of donor HSC using chemotherapy regimen without total-body irradiation. The HSC are derived from either related donor or unrelated UCB or haploidentical donor.

**Solid tumors**

Chemotherapy and radiation therapy of solid tumors often destroy patient’s HSC. They can be replaced with peripheral blood, bone marrow or UCB HSC transplant. Clinical trials NCT00436761 and NCT00112645 are examining different pretreatment regimens in order to decrease the incidence of side effects following HSC transplantation, mainly acute and chronic graft versus host disease.

**Stroke**

Stroke is rapid loss of brain functions due to disturbance in the blood supply to the brain. Preclinical studies have suggested that CD34+ cells isolated from UCB can produce limited functional recovery in animal stroke models. The purpose of the clinical trial
NCT01438593 is to determine the safety and possible effectiveness of brain transplants of CD34+ stem cells from UCB for the treatment of stroke.

Systemic lupus erythematosus and systemic sclerosis

Systemic lupus erythematosus and systemic sclerosis are autoimmune diseases, where a patient’s immune system attacks and damages its own body. Over the past 15 years, >1500 patients have received HSC transplant, mostly autologous bone marrow, as treatment for a severe autoimmune diseases. Recent retrospective analysis of 900 patients showed that 85 of them were treated for systemic lupus erythematosus and 175 for systemic sclerosis. However, data are difficult to interpret due to different treatment regimens, source of HSC, non-standardized outcome measures and lack of long-term follow-up. The purpose of the clinical study NCT00684255 is to determine if a reduced intensity non-myeloablative chemoimmunotherapy followed by allogeneic stem cell transplantation of matched family donors and matched unrelated UCB donors will be well tolerated in medically refractory systemic lupus erythematosus and systemic sclerosis.

Conclusion

UCB stem cells have reached the point of being recognized as a proven therapy for hematological disorders. In November 2011, the US Food and Drug Administration approved Hemacord®, the first licensed UCB stem cell therapy indicated for use in HSC transplantation procedures for patients with hematopoietic disorders.

As a rich source of the most primitive HSCs, UCB has a strong regenerative potential in stem cell-based-therapy for hematological disorders. Although UCB stem cell transplants can ameliorate symptoms in a variety of conditions and benefit patients, it is, however, highly unlikely that they can provide a cure for any non-hematological disorders. UCB stem cells are primarily HSCs and although there are numerous reports that they can differentiate into a variety of other cell lineages, the yield is low and there is a lack of functional data both in vitro and in vivo that would support their application in human therapy. Regardless, the potential use of UCB stem cells in therapy for a variety of non-hematological disorders, from neurodegenerative diseases to liver cirrhosis, is ever expanding and the number of clinical trials is increasing. Therapeutic success depends upon many factors beyond the stem cells themselves and it is still unclear how clinically meaningful
prospective benefits of UCB stem cell-based therapy are for most of the non-hematological disorders currently in clinical trials.

**Acknowledgement**

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**References**


